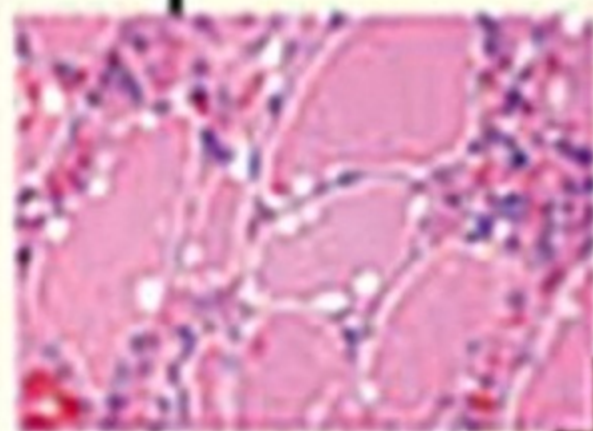


Essentials of Pediatric Oral Pathology

Mayur Chaudhary
Shweta Dixit Chaudhary



Forewords
Asha Singh
Minal Chaudhary

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Essentials of **PEDIATRIC ORAL PATHOLOGY**

Essentials of PEDIATRIC ORAL PATHOLOGY

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Essentials of Pediatric Oral Pathology

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our beloved parents

Shri Bhasker Chaudhary and Smt Maya Chaudhary

Shri Shivendra Dutt Dixit and Smt Manju Dixit

and our dearest daughter

Tvisha Chaudhary

whose constant support and encouragement

have been a guiding light for us.

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Foreword

I would like to heartily congratulate Drs Mayur Chaudhary and Shweta Dixit Chaudhary for their timely recognition of the need for a piece of literature dedicated to *Essentials of Pediatric Oral Pathology*.

This book is the first of its kind and I have felt paucity of a book of this nature while teaching my postgraduate students. The inspiration to write such a book probably stems from one of the countless discussions that I have had with my postgraduate student Shweta Dixit.

The book consists of fifteen chapters including all the common oral pathologies in children. The chapter on *Caries* includes pathology, prevention and treatment aspects of caries in detail.

I am extremely proud to be a part of the pioneer book on the subject of pediatric oral pathology, and I am sure that the hard work, dedication and sincerity of the authors will be all and transparent to any student reading through this book. I wish the authors all success in this brilliant endeavor of theirs.



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Foreword

It is only in the past couple of decades that pediatric dentistry has come of age. There is an increasing awareness in the minds of parents regarding the importance of deciduous dentition and its associated disease conditions. This has led to an increase in the number of patients in the pediatric age-group seeking treatment.

The distinct environments and requirements of the child patient create a necessity for a book exclusively based on pediatric oral pathology. Thus, there is a definite need for a separate book dealing specifically with the diagnosis and treatment of diseases of the young.

Essentials of Pediatric Oral Pathology by Drs Mayur Chaudhary and Shweta Dixit Chaudhary caters to this particular need. It is an easy-to-refer book with elaborate illustrations, latest treatment modalities as well as lucid elaboration of clinical features.

The authors have also included a separate chapter on *Pediatric Forensic Odontology*, which should be of great help to the reader. I am sure that this well-written book will be of immense help to teachers and students alike.



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Preface

Pediatric dentistry is amongst the youngest of the branches of dentistry, yet has grown by leaps and bounds to command one of the highest summits in dentistry. This book is a minuscule contribution to this effort.

It has been our dedicated and sincere effort to work within the limits of this book and concentrate on the more relevant topics as far as possible. The topics are covered on the basis of the frequency at which a particular lesion is seen in the pediatric population.

Numerous pathological entities including the commonly occurring ones, e.g. dental caries, infectious diseases, etc. and some rare entities, e.g. salivary glands, bone, skin, etc. have been explained in a simplified manner in context with children.

A chapter on *Forensic Odontology in Children* has been included which also deals with the currently relevant topics of child abuse and neglect. Each chapter has been provided with adequate and to-the-point references for greater exploration of the topic by young enthusiastic minds.

To distinguish between normal and pathology, one must be well-versed with the physiology. Keeping this fact in mind, comprehensive appendices defining the normal values of various aspects in children have been included.

We hope that this piece of work occupies the vacant niche for a comprehensive book on Pediatric Oral Pathology.

To err is human, to forgive is divine

With these words, we wish to admit that no one is ever perfect just as we are not. There might be some shortcomings despite our most sincere efforts. The reader's suggestions for further improvements shall be greatly encouraged and acknowledged.

Mayur Chaudhary
Shweta Dixit Chaudhary

Acknowledgments

We stand with our heads bowed to the almighty God for giving us the opportunity to undertake the writing of this book and carry to its successful completion.

The writing of a book is an arduous undertaking and is impossible without the timely and sequential involvement of an entire team. We wish to express our sincere gratitude to all the contributors whose inputs have added character to the book.

Our respected teachers Dr Asha Singh, Dr Meena Kulkarni and Dr Rajeev Desai have provided us the basic understanding and knowledge of the subject and have always stood us in good stead.

The skilled technicians, artists, reviewers and the entire panel of M/s Jaypee Brothers Medical Publishers (P) Ltd deserves a standing ovation for their tireless efforts in designing and refining the vast host of minute details in the book.

A special thanks to Shri Vijay Gulhane and Shri Vipin Sharma who have been a reassuring buttress in all our times of doubt and hesitation.

We sincerely wish to acknowledge the overwhelming support provided to us by the staff and students, especially Dr Ashok Patil, Dean, SMBT Dental College and Hospital, Sangamner, Maharashtra, India and Dr Anil Ghom, Professor and Head, Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Research Institute, Rajnandgaon, Chhattisgarh, India.

Thanks to all those who have directly or indirectly helped us in this venture and last but not least, we would like to thank our parents and family members for their ever-extended arms of support.

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Introduction

As *Bruno Bettelheim* once remarked, “Raising children is a creative endeavor, an art rather than a science”, all of us who know about the advent of dentistry right from the ages of the tooth worm theory to the present scenario where dentistry is brimming with new techniques and newer materials would agree with him. Dentistry started from a single department in various schools and universities to branch into various specialties, with post graduate and diploma courses in individual specialties. At this juncture in the steep development curve of dentistry, this book aims to explore yet another aspect of dentistry, i.e. pediatric oral pathology.

DEFINITION OF PEDIATRIC DENTISTRY

According to the American Academy of Pediatric Dentistry (AAPD), Pediatric dentistry is an age-defined specialty that provides primary and comprehensive, preventive and therapeutic oral health care for infants and children through adolescence, including those with special health care needs.

This gives us answers for the following questions:

- **Who are the objects of pediatric dentistry?**
 - Infants and children through adolescence.
 - Including those with special health care needs.
- **What does pediatric dentistry provide?**
 - Provides both primary and comprehensive preventive oral health care.
 - Provides both primary and comprehensive therapeutic oral health care.
- **What are the key elements of this definition that make it so unique?**
 - *Age-defined:* Most specialties are procedure-defined (endodontics, periodontics, etc.). Pediatric dentists provide care for their specific age group of patients. There is no limitation to what type of treatment they provide.
 - *Primary and comprehensive care:* Pediatric dentists are primary providers. There is no need for a referral of patients. Parents can choose to have their children evaluated and treated by a pediatric dentist just like they can choose to have their child treated by a pediatrician.
 - *Infants and children through adolescence:* Pediatric dentists see patients at any age from birth up to their late teens.
 - *Special health care needs:* Pediatric dentists have the training and experience to evaluate and treat patients, that are medically compromised. This includes patients with hemophilia, leukemia, congenital syndromes, etc. No other dental specialty, other than oral and maxillofacial surgery is more involved in hospital care of patients.

We have talked about the four key elements in the definition that make the pediatric dentists so unique, and most of all it is treatment provided with *tender, loving care*.

The primary focus of most dental specialties is a particular area of dental, oral, or maxillofacial expertise. Pediatric dentistry encompasses a variety of disciplines, techniques, procedures and skills that share a common basis with other specialties, but are modified and adapted to the unique requirements of infants, children, adolescents and those with special health care needs. By being an age specific specialty, pediatric dentistry encompasses disciplines such as behavior guidance, care of the medically and developmentally compromised and disabled patient, supervision of orofacial growth and development, caries prevention, pharmacological management and hospital dentistry as well as other traditional fields of dentistry. These skills are applied to the needs of children throughout their ever changing stages of development and to treat conditions and diseases unique to growing individuals.

The AAPD founded in 1947, is the membership organization representing the specialty of pediatric dentistry. The membership provides care to millions of infants, children, adolescents and persons with oral health care needs. They are primary contributors to professional education programs and publications on pediatric oral health.

ORAL PATHOLOGY

HISTORY

Oral pathology appears to have had its origin during the first Golden Age of Dentistry, from 1835 through the organization of the American Dental Association in 1860. This era saw the establishment of organized, education-based dentistry and was integrally associated with an obvious fascination for pathologic processes and an inherent wish to share scientific and clinical knowledge with others in the dental profession. It encompassed the creation of the professorship of “Dental Pathology.”

In the practice of medicine, three main questions are given utmost consideration:

1. What is wrong? (Diagnosis)
2. What is going to happen? (Prognosis)
3. What can be done? (Treatment)

To this, two more questions should be added:

1. How did this happen? (Etiology)
2. Why did this happen? (Pathogenesis)
 - Most of the times, diagnosis of a specific lesion depends upon the histopathologic examination of the same under the microscope.
 - Secondly, the cause and effect of the disease can be better understood (extent of the lesion).

DEFINITION

Basically, oral pathology is a science of dentistry that deals with the etiology, pathogenesis, management and prognosis of various diseases affecting oral and paraoral structures as well as local and systemic effects of various diseases as reflected in the oral cavity, diagnosis of various diseases, disorders and lesions under the microscope.

PEDIATRIC ORAL PATHOLOGY

The Pediatric Oral Pathology (POP) seminars began in 1977 as a joint, interstate effort between the Department of Dentistry, Pittsburgh Children’s Hospital, Pittsburgh, Pennsylvania (USA) and the Department of Oral Pathology, West Virginia University School of Dentistry, Morgantown, West Virginia. They were intended to provide hands-on discussion opportunities for pediatric dentistry residents interested in lesions of the orofacial region in children and young adults. Weekly afternoon seminars were offered during the Fall Semester in Children’s Hospital of Pittsburgh, with Dr Jerry Bouquot, Chairman of the WVU Department of Oral Pathology, presiding as monitor and discussion leader.

The seminars are participation discussions of clinical cases, with participants being provided “notebook cases” a week ahead of time, with appropriate photos, historical and clinical information provided. Participants are expected to come to the next seminar with a differential diagnosis, a diagnostic work-up plan and a management plan for each case. They are called upon individually to treat the cases, as best as they can within the limits of the format, as their own patients. Each seminar encompasses lesions which can be included in a similar differential diagnosis category. From time to time, special topics are provided in a more traditional lecture format, and these may carry over several seminars. As of June, 2000, there had been discussion of more than 960 clinical cases.

DEFINITION

Pediatric Oral Pathology is an art and science of dentistry that deals with the etiology, pathogenesis, management and prognosis of various diseases and developmental anomalies affecting oral and paraoral structures of infants, children through adolescence and encompass primary and comprehensive, preventive and therapeutic oral health care through variety of disciplines, techniques, procedures, and skills that are modified and adapted to the unique requirements of infants, children, adolescents, and those with special health care needs.

These are one of the few milestones in the journey of the art and science of pediatric oral pathology, a subject which should be read and comprehended by:

- Pediatric dentists
- Oral pathologists
- Students of dentistry
- General dental practitioners and other dental specialists
- Government agencies and health care policymakers
- Individuals interested in the health of children.



Chapter 1



Developmental Disturbances in Children

Mayur Chaudhary, Shweta Dixit Chaudhary, Prashant Dixit

CHAPTER OVERVIEW

Introduction

Can be broadly divided as:

- I. Those affecting the oral and paraoral structures excepting the teeth
- II. Those affecting the teeth

Those affecting the oral and paraoral structures excepting the teeth may be further divided as:

1. Developmental disturbances of jaws:
 - Agnathia
 - Micrognathia
 - Macrognathia
 - Facial hemihypertrophy
 - Facial hemiatrophy
2. Developmental disturbances of lips and palate:
 - Congenital lip pits and fistula
 - Commissural lip pits
 - van der Woude syndrome
 - Cleft lip and cleft palate
 - Cheilitis glandularis
 - Cheilitis granulomatosa
 - Peutz-Jeghers syndrome
 - Labial and oral melanotic macule
3. Developmental disturbances of the oral mucosa:
 - Fordyce's granules
 - Focal epithelial hyperplasia
4. Developmental disturbances of the gingiva:
 - Fibromatosis gingivae
 - Retrocuspid papilla
5. Developmental disturbances of the tongue:
 - Aglossia and microglossia
 - Macroglossia
 - Ankyloglossia or tongue tie
 - Cleft tongue
 - Fissured tongue
 - Median rhomboid glossitis
 - Benign migratory glossitis
 - Hairy tongue
 - Lingual varices
 - Lingual thyroid nodule

6. Developmental disturbances of oral lymphoid tissue:

- Reactive lymphoid aggregate
- Lymphoid hamartoma
- Angiolymphoid hyperplasia with eosinophilia
- Lymphoepithelial cyst

7. Developmental disturbances of the salivary glands:

- Aplasia
- Xerostomia
- Hyperplasia of palatal glands
- Atresia
- Aberrancy
- Developmental lingual mandibular salivary gland depression
- Anterior lingual depression

Those affecting the teeth may be further divided as:

1. Developmental defects in size of teeth:
 - Microdontia
 - Macrodontia
2. Developmental defects in shape of teeth:
 - Gemination
 - Fusion
 - Concrescence
 - Dilaceration
 - Talon's cusp
 - Dens in dente
 - Dens evaginatus
 - Taurodontism
 - Supernumerary roots
3. Developmental defects in number of teeth:
 - Anodontia
 - Supernumerary teeth
 - Predeciduous dentition
4. Developmental defects in structure of teeth:
 - Amelogenesis imperfecta
 - Environmental enamel hypoplasia
 - Dentinogenesis imperfecta
 - Dentin dysplasia
 - Regional odontodysplasia
 - Dentin hypocalcification

5. Defects of growth (eruption) of teeth:

Premature eruption
Eruption sequestrum
Delayed eruption
Multiple unerupted teeth
Embedded and impacted teeth
Ankylosed deciduous teeth

6. Fissural cysts of the oral region:

Nasopalatine duct cyst

Median palatal cyst

Globulomaxillary cyst

Median mandibular cyst

Nasoalveolar cyst

Palatal and alveolar cysts of newborns

Thyroglossal tract cyst

Epidermal inclusion cyst

Dermoid cyst

Heterotopic oral gastrointestinal cyst

INTRODUCTION

Developmental disturbances comprise a group of disorders that are manifested during the early months of gestation. They may be genetically determined, environmentally determined or may exhibit a role of both genetic and environmental factors. These disorders may resolve after few months or may persist forever. The disorders may be termed congenital when present at birth and hereditary when transmitted from one generation to another. Special attention is to be given to the term anomaly which means irregularity or different from normal.

This chapter focuses on some of the developmental disturbances and anomalies pertaining to children.

DEVELOPMENTAL DISTURBANCES OF JAWS

- Agnathia
- Micrognathia
- Macrognathia
- Facial hemihypertrophy
- Facial hemiatrophy.

AGNATHIA

Definition

A lethal anomaly characterized by hypoplasia or absence of the mandible with abnormally positioned ears and any form of holoprosencephaly (Fig. 1.1).

Etiology

- May be due to autosomal recessive inheritance.
- Sporadic cases without inheritance have also been seen.

Pathogenesis

Agnathia probably results due to failure of migration of neural crest mesenchyme into the maxillary prominence at the fourth to fifth week of gestation (post-conception). When it is not associated with central nervous system malformations it is referred to as “agnathia-microstomia-synotia.”



FIGURE 1.1: Agnathia showing ears fused in the midline, complete absence of the mandible and clefting of both lips

MICROGNATHIA

Micrognathia implies a small jaw and may affect either the maxilla or mandible. Lannelongue and Menard first described Pierre Robin syndrome in 1891 in a report on two patients with micrognathia, cleft palate and retroglossoptosis.¹ In 1926, Pierre Robin published the case of an infant with the complete syndrome.² Until 1974, the triad was known as Pierre Robin syndrome; however, the term syndrome is now reserved for those errors of morphogenesis with the simultaneous presence of multiple anomalies caused by a single etiology.

Pathogenesis

- Autosomal recessive inheritance is possible. An X-linked variant has been reported involving cardiac malformations and clubfeet.

- Acquired type of micrognathia is of postnatal origin and usually results from a disturbance in the area of the temporomandibular joint. Trauma and infection may lead to ankylosis of the joint which may result in varying degrees of micrognathia.
- Three pathophysiological theories exist to explain the occurrence of Pierre Robin sequence.
 1. The mechanical theory: This theory is the most accepted. The initial event, mandibular hypoplasia, occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios could play a role in the etiology since the lack of amniotic fluid could cause deformation of the chin and subsequent impaction of the tongue between the palatal shelves.
 2. The neurological maturation theory: A delay in neurological maturation has been noted on electromyography of the tongue musculature, the pharyngeal pillars and the palate, as has a delay in hypoglossal nerve conduction. The spontaneous correction of the majority of cases with age supports this theory.
 3. The rhombencephalic dysneurulation theory: In this theory, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

Clinical Features

- This heterogeneous birth defect has a prevalence of approximately 1 per 8500 live births.
- The male-to-female ratio is 1:1, except in the X-linked form.
- Micrognathia is reported in the majority of cases (91.7%). It is characterized by retraction of the inferior dental arch, 10 to 12 mm behind the superior arch (Fig. 1.2).
- The mandible has a small body, obtuse gonial angle, and a posteriorly located condyle. The growth of the mandible catches up during the first year; however, mandibular hypoplasia resolves and the child attains a normal profile approximately by the age 5 to 6 years.
- However, due to posterior positioning of the mandible with regard to the skull, retrusion of the jaw may be apparent.
- Glossoptosis is noted in 70 to 85 percent of reported cases. Macroglossia and ankyloglossia are relatively rare findings.

Since the frequency of diagnosis of *macrognathia*, *facial hemihypertrophy* and *facial hemiatrophy* is less in the pediatric population and are generally diagnosed in adulthood, these have not been explained in detail here.



FIGURE 1.2: Micrognathia showing an underdeveloped mandible



FIGURE 1.3: Congenital lip pits on the lower lip

DEVELOPMENTAL DISTURBANCES OF LIPS AND PALATE

- Congenital lip pits and fistula
- Commissural lip pits
- van der Woude syndrome
- Cleft lip and cleft palate
- Cheilitis glandularis
- Cheilitis granulomatosa
- Peutz-Jeghers syndrome
- Labial and oral melanotic macule

CONGENITAL LIP PITS AND FISTULA

Congenital lip pits and fistula may occur due to notching of the lip at an early stage of development with fixation of tissue at the base of the notch.

Clinical Features

- They may be unilateral or bilateral.
- Most commonly occur on the lower lip (Fig. 1.3).
- Sometimes, a mucous secretion may exude from the base of the pit which may be due to saliva from minor salivary glands draining into the depth of the invagination.



FIGURE 1.4: Bilateral congenital lip pits at the commissural area

COMMISSURAL LIP PITS

These are mucosal invaginations occurring at the corners of the mouth on the vermillion border.

Pathogenesis

- They follow a hereditary pattern and may occur alone or in association with other developmental anomalies most possibly following a Mendelian dominant inheritance.
- They mostly occur due to incomplete/failure of normal fusion of maxillary and mandibular processes.

Clinical Features

- Taylor and Lane, 1966,³ and McConell, 1970,⁴ reported that 75-80 percent of the cases of lip pits were associated with cleft lip or cleft palate.
- Commissural lip pits are same as congenital lip pits but occur at the lateral commissures of lip (Fig. 1.4).
- Prevalence in children ranges from 0.2 to 0.7 percent.⁵
- They may be unilateral or bilateral.
- Most commonly occur at the corners of the mouth.
- Sometimes, a mucous secretion may exude from the base of the pit which may be due to saliva from minor salivary glands draining into the depth of the invagination.

Histopathologic Features

- Lesional area shows a narrow invagination lined by stratified squamous epithelium.
- Few areas show ducts of minor salivary glands.

Management

1. No specific treatment is required.
2. Surgical excision may be recommended if the pits get secondarily infected.

VAN DER WOUDE SYNDROME

van der Woude syndrome (VWS) is an autosomal dominant syndrome, single gene disorder showing high penetrance and variable expressivity that typically consists of a cleft lip or cleft palate and/or distinctive pits of the lower lips. It was characterized in 1954.⁶

Etiopathogenesis

- This is an autosomal dominant syndrome with a penetrance of 75 percent. But penetrance was recorded to be 100 percent when supposedly unaffected carriers were closely examined for minor expressions of the syndrome.
- Viral infections may result in an interference with the IRF6 gene which is involved in the immune response to viral infections.
- *De novo* mutations may lead to single nucleotide polymorphism resulting in a defect leading to the features of van der Woude syndrome.
- The gene isolated for van der Woude syndrome is 1q32 to q41.
- A second modifying gene is 17p11.2-p11.1 with a second chromosome locus being 1p34.
- The Interferon Regulatory Factor-6 (IRF-6) is the specific gene responsible for VWS. This gene has been found to regulate fetal craniofacial development in mice.

Clinical Features

- Lower lip pits
- Incomplete unilateral cleft lip
- Cleft lip with or without cleft palate
- Bilateral cleft lip and palate (Fig. 1.5)
- Isolated cleft palate
- Submucosal cleft palate
- Bifid uvula may occur as an isolated finding
- Cleft lip and palate
 - Cleft lip and palate may be isolated, unilateral or bilateral.
 - Submucous cleft palate leads to hypernasal voice.
- Lip pits
 - Lower lip pits are fairly distinctive and usually medial.
 - May be associated with accessory salivary glands.
 - Saliva, either visible or expressible, may be present.
 - Lip pits, at times, could be the only manifestation of the syndrome.



FIGURE 1.5: Bilateral cleft lip in van der Woude syndrome

- **Teeth**
Individuals may have hypodontia, most commonly manifested as missing maxillary lateral incisors or maxillary or mandibular second premolars. Again, this may be the only manifestation of the syndrome.
- **Other oral manifestations:**
 - Syngnathia (congenital adhesion of the jaws).
 - Narrow, high arched palate.
 - Ankyloglossia (short glossal frenulum or tongue-tie).
- **Extraoral manifestations:**
 - Limb anomalies
 - Popliteal webs
 - Brain abnormalities
 - Accessory nipples
 - Congenital heart defects
 - Hirschsprung disease
- Features of van der Woude syndrome have been seen in individuals with popliteal pterygium syndrome, which has also been linked to mutations in the same gene.

Management

1. **Primary care**
 - Enquiry about family history of genetic disorders.
 - Detailed ultrasonography scan at 10–14 weeks of pregnancy.
 - Examination and genetic counseling by a pediatric geneticist (dysmorphologist) is suggested.
 - Regular antenatal check up.
 - Restricted fragment length polymorphism (RFLP) may be done

2. **Secondary care**
 - Retraction of premaxilla – 7–8 weeks (Stage I)
 - Obturator is given till the surgery for cleft is planned and executed to help the patient in eating (Stage I)
 - Maxillary arch expansion is done at the completion of deciduous dentition (Stage I)
 - Buccal crossbite correction—4–6 years (Stage II)
 - Anterior teeth are aligned—8–9 years (Stage III)
 - Final orthodontics—11+ years (Stage III)

3. Tertiary care

Restorative procedures

4. Surgical care

- Surgical repair of cleft lip and palate or other anomalies.
 - *Lip repair procedures* (Cheiloplasty) – Elaborated by Rose, Mirault, Le Mesurier, Tennison, Millard.
 - *Palate repair procedures* – von Langenback, Veau-Wardill Kilner (V-Y pushback), Two flap palatoplasty, Double opposing Z plasty, posterior pharyngeal flap for submucous cleft palate.
 - Surgical excision of lip pits - either to alleviate discomfort or for cosmetic reasons.

Sequelae to untreated deformity/anomaly:

1. Feeding difficulties
2. Malocclusion
3. Speech/Voice disorders
4. Esthetics
5. Frequent otitis media
6. Hearing loss.

CLEFT LIP AND CLEFT PALATE

Millions of children and adults suffer from the social enigma of cleft lip and palate, battling to live a life of dignity. Failure of fusion of palatal shelves, septum and primary palate, which normally takes place between the 8th and 17th week of embryologic development leads to the formation of a cleft.

Development of Palate

The organization of the face requires tissues to proliferate, fuse and differentiate. The polarizing signal candidates expressed in craniofacial primordia include sonic hedgehog (shh), its putative receptor patched, fibroblast growth factor 8 (FGF-8) and bone morphogenetic protein 2 (BMP-2).⁷ Evidence exists that the teratogen, retinoic acid exerts some of its effects on craniofacial development through the disruption of the shh signaling pathway. Transforming growth factor -3 (TGF -3) also has a broad spectrum of biological activities.

In humans, palate development begins towards the end of the fifth week of intrauterine life and is complete at about twelve weeks. The critical period is from the end of the sixth week to the beginning of the ninth week. In normal palate development, mesenchymal cells from the neural crest migrate to the primitive oral cavity forming the maxillary processes in association with the craniopharyngeal ectoderm.⁸

The primary palate arises from the fusion of two medial nasal prominences that form the intermaxillary segment, which develops towards the end of the fifth week of intrauterine life in humans. It consists of two portions: a labial component that forms the philtrum of the upper lip and a triangular palatal component of bone that includes the four maxillary incisor teeth. The primary palate extends posteriorly to the incisive foramen. In humans, the secondary palate comprises at least 90 percent of the hard and soft palates. Development of the intact secondary palate is a dynamic process which has been arbitrarily split into three stages. Stages I to III namely Figs 1.6 and 1.7). **Stage I** of secondary palate development is characterized by formation of the palatal shelves from the maxillary processes. These shelves are orientated vertically, either side of the developing tongue. It is not known why the shelves attain this vertical orientation. Ferguson, 1981, proposed that the direction of shelf growth be related to the amount of space available in the oronasal cavity during the period of palatogenesis.⁹

At a precise developmental stage (**Stage II**), these vertical palatal shelves elevate to a horizontal position above the dorsum of the tongue.¹⁰ This event occurs rapidly, possibly in a matter of hours.

Stage III of secondary palate development involves fusion of the medial edge epithelium (MEE) of the approximating palatal shelves with each other via numerous desmosome contacts to form a midline palatal seam. This then separates the oral and nasal cavities. Keratin fibrils and desmosomes are upregulated in the medial edge epithelium seam at this point, presumably to strengthen the bond between the newly adherent medial edge epithelium cells. This seam rapidly degenerates, a process characterized by loss of complex cytokeratins and basement membrane components such as laminin and desmosomes and by an increase of vimentin-rich connective tissue, tenascin, proteoglycan and collagen expression. Medial edge epithelium degeneration allows mesenchymal cells to flow across the now intact horizontal palate. There have been several theories on the mechanism(s) of medial edge epithelium degeneration. Shapiro and Sweney, 1969, suggested that it occurred as a result of programmed cell death.¹¹ Gartner et al, 1978, disputed this on the grounds that there was no evidence of any cellular debris or phagocytic activity at any time during this process.¹² Furthermore, some evidence of metabolic activity occurring within so-called apoptotic cells was described. A radical

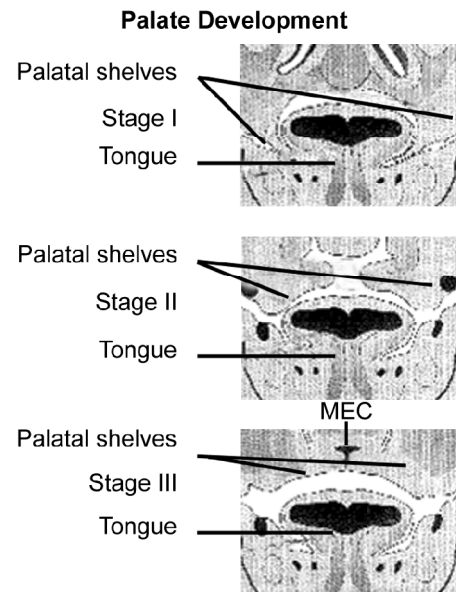


FIGURE 1.6: Schematic diagram of coronal section through a developing face showing three stages of secondary palate development. At stage I, the palatal shelves are vertical, they elevate in stage II and fuse in stage III

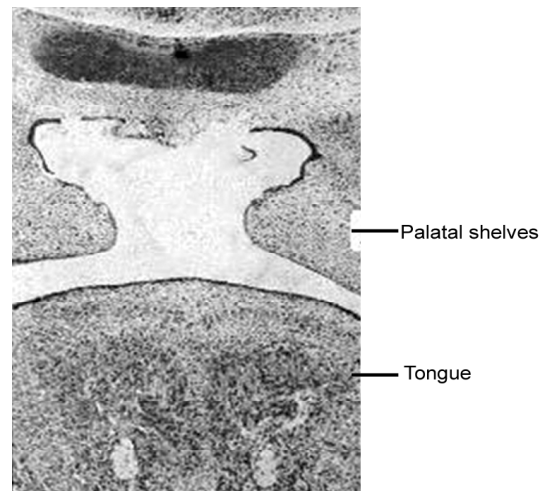


FIGURE 1.7: Hematoxylin and eosin stained section of a developing fetus where the palatal shelves have elevated with the tongue lying inferiorly. Although there has been elevation, the shelves have still to fuse

postulate by Fitchett and Hay, 1989, offered the possibility that the medial edge epithelium cells migrate into the body of the mesenchyme and transform into mesenchymal cells.¹³ This process is known as epithelial-mesenchyme transformation (EMT). An alternative view is that medial edge epithelium cells migrate nasally and orally out of the medial edge epithelium seam and become incorporated into the oral and nasal epithelia on the palatal surface.

On completion of stage III, the epithelia on the nasal aspect of the palate are pseudostratified ciliated columnar cells whilst those on the oral aspect of the palate are stratified squamous, non-keratinizing cells.

Cleft palate may result from disturbances at any stage of palate development like defective palatal shelf growth, delayed or failed shelf elevation, defective shelf fusion, failure of medial edge epithelium cell death, post-fusion rupture and failure of mesenchymal consolidation and differentiation. Sun et al, 1998a, suggested that lack of intimate palatal shelf contact after elevation is one possible cause and recent research into palate development has concentrated on fusion of the shelves rather than elevation.¹⁴ Ferguson, 1981, on the other hand, took the view that failure of palatal shelf elevation may be responsible for 90 percent of palatal clefting.

Palatal shelf elevation: In principle, an intrinsic force generated within the palatal shelves reaches a threshold level which exceeds the force of resistance culminating in shelf elevation. Elevation of the palatal shelves is rapid with a swinging 'flip-up' mechanism in the anterior one-third of the palate and an oozing remodeling 'flow' mechanism in the posterior two-thirds of the palate.

Etiopathogenesis

- Isolated clefts are those that are associated with no other birth anomaly.
- Syndromic clefts are those associated with other birth disorders.
- Clefts are a feature of over 660 syndromes and most are rare.

More common syndromes: Pierre-Robin sequence, Crouzon, Apert, Pfeiffer, van der Woude, Treacher Collins, Velocardiofacial. Syndromal clefts makes up 15 percent of cleft lip +/- palate.

Isolated clefts are caused by an interaction between an individual's genes and certain environmental factors (often impossible to identify). Phenytoin, accutane, alcohol, tobacco, folic acid and pyridoxine deficiencies have also been associated with clefting.¹⁵

Increasing parental age, especially an older father, is also associated. About 35 percent of clefts have a positive family history.

Incidence of Clefting

There are significant ethnic differences in the prevalence of cleft lip and palate, with the highest rates in Asian populations and Native Americans, intermediate rates in Caucasians and lowest rates in African Americans.¹⁶⁻¹⁸

Clefting in US 1:750 births

Asians 2.1:1000 or 1:500

Caucasians 1:1000 to 1:750¹⁹

TABLE 1.1: Percentile familial distribution of cleft lip and palate

<i>Relationship to index case</i>	<i>Cleft lip/palate</i>	<i>Cleft palate¹⁵</i>
Siblings (overall risk)	4.00%	1.80%
Siblings (no other affected)	2.20%	-
Siblings (2 affected siblings)	10.00%	8.00%
Siblings and affected parents	10.00%	-
Children	4.30%	6.20%
Second degree relatives	0.60%	-
Third degree relatives	0.30%	-
General population	0.10%	0.04%

UK 1: 1000

Blacks 0.41:1000 or 1:1200

Clefts can occur as cleft lip alone, cleft lip/palate, or cleft palate alone (Table 1.1)

Cleft lip alone: 21 percent of clefts

Cleft lip/palate together: 46 percent of clefts

Cleft palate alone: 33 percent of clefts

Bilateral cleft lip is associated with a cleft palate in 86 percent of cases

Clefts occur more commonly in boys than in girls

Inheritance: Inheritance is variable depending on whether a syndrome is associated and when it is, depending on the syndrome present. It could be autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, non-Mendelian inheritance.

Classification

Veau classification of clefts of the lip: The severity of cleft lip can range from microform (very small defect) to complete clefts and be unilateral or bilateral. Cleft lip will usually result in minor deformity of the nose characterized by a flattened nostril on the affected side and flaring of the base on the affected side. Cleft lip can involve the alveolus, in which case it has involved the primary palate.

If there is a bilateral cleft of the lip, there may be extension of the premaxillary segment.

Class I—A unilateral notching of the vermilion not extending into the lip

Class II—A unilateral notching of the vermilion border, with the cleft extending into the lip but not including the floor of the nose

Class III—A unilateral clefting of the vermilion border of the lip extending into the floor of the nose

Class IV—Any bilateral clefting of the lip, whether it be incomplete notching or complete clefting.²⁰

Veau classification of clefts of the palate: Cleft palate can occur with cleft lip or less often by itself. Some patients will

present with submucous clefts where the mucosal lining of the oral cavity roof is present without appropriate supportive bone and muscle structure. Signs of submucous clefting include a bifid uvula, diastasis of soft palate musculature (division of muscles along midline) and notch in hard palate.

Veau divided palatal clefts into four classes as follows:

Class I—Involves only the soft palate.

Class II—Involves the hard and soft palates but not the alveolar process.

Class III—Involves both the hard and soft palates and the alveolar process on one side of the premaxillary area.

Class IV—Involves the soft palate and continues through the alveolus on both sides of the premaxilla, leaving it free and often mobile.²¹

Kernahan and Stark, 1958 and Spina, 1974, have classified cleft lip and palate depending on embryological principles.

Kernahan and Stark classification²¹

Group I: Cleft of the primary palate only

- Unilateral
- Bilateral
- Total
- Subtotal

Group II: Cleft of the secondary palate only

- Total
- Subtotal
- Submucous

Group III: Cleft of the both primary and secondary palate

- Unilateral—Total, Subtotal
- Median—Total, Subtotal
- Bilateral—Total, Subtotal

Spina classification²¹

Group I: Pre-incisive foramen clefts

- Unilateral
- Bilateral
- Median (cleft of the lip with or without an alveolar cleft)—Total, Partial

Group II: Transincisive foramen clefts (cleft of the lip, alveolus and palate)

- Unilateral
- Bilateral

Group III: Post-incisive foramen clefts

- Total
- Partial

Group IV: Rare facial clefts.

Kernahan, 1971, has proposed stripped Y classification for rapid graphic presentation of the defect. This was subsequently modified by Ehlsaky, 1972 and Millard, 1976.²¹

The variation in clefts is considerable. A good way to record a cleft lip is by photography. A better way to record a palatal cleft is to fill in the following figure with stripes and dots.

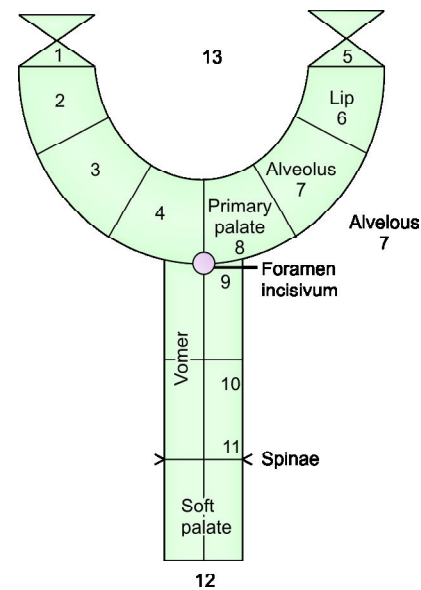


FIGURE 1.8A: Diagrammatic representation of Kernahan classification for clefts

- 1, 5 : Nasal floor
- 2, 6 : Lip
- 3, 7 : Alveolus
- 4, 8 : Hard palate anterior to incisive foramen
- 9, 10 : Hard palate posterior to incisive foramen
- 11 : Soft palate
- 12 : Congenital velopharyngeal incompetence without obvious clefts
- 13 : Protrusion of premaxilla

In the stripped Y classification, the involved area is shaded by pen to graphically represent the defect (Figs 1.8A and B).

Categories of Clefts

Depending on the elemental characteristics of the embryology, anatomy and physiology of the cleft defect, the varieties of clefts of the lip and palate may be tabulated into four general categories:

1. Those involving the lip and alveolus
2. Those involving the lip and palate
3. Those in which the palate alone is affected
4. Congenital insufficiency of the palate

The term 'palate' will include both the hard palate and the velum or soft palate.

Genetic Basis of Nonsyndromic Cleft Lip and/or Palate

Fogh-Anderson, 1942, provided the first population-based evidence that CL $\pm$ P has a strong genetic component.²²

- Cleft lip and palate syndromes in humans are associated with polymorphisms in the gene (TGF β) encoding transforming growth factor- α (TGF α), an epidermal growth factor receptor (EGFR) ligand made by most epithelia.

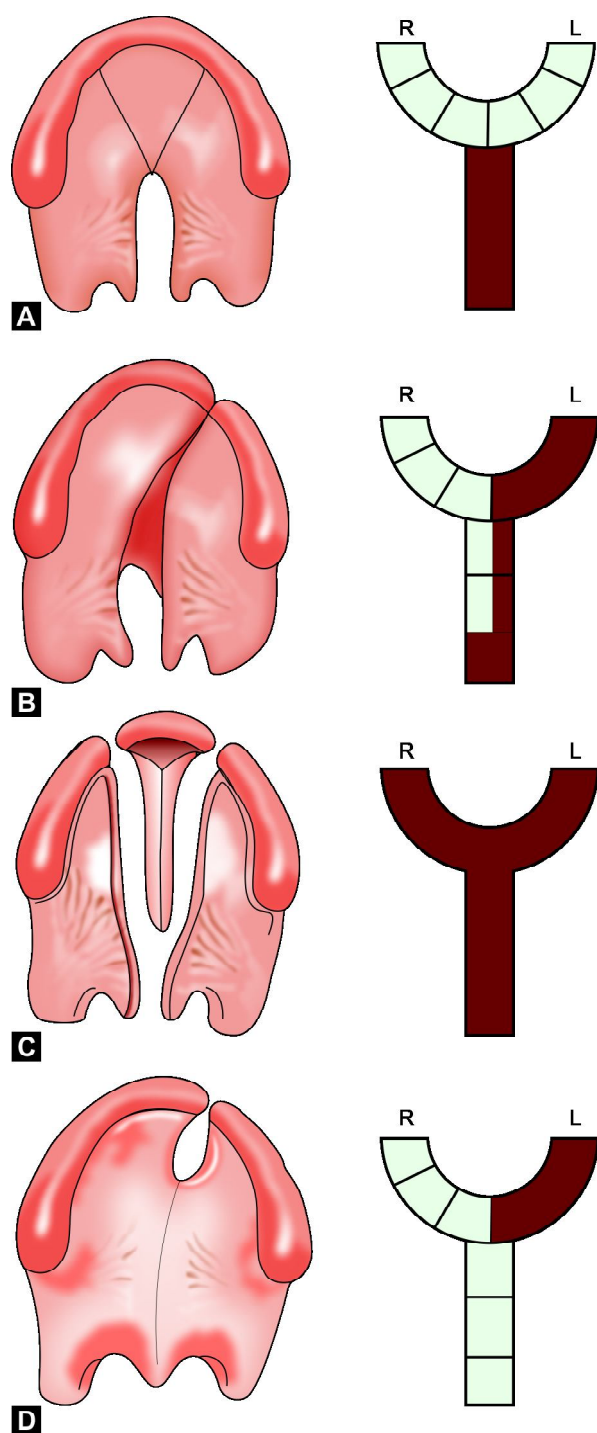


FIGURE 1.8B (A to D): Diagrammatic representation of Kernahan classification for clefts

- A : Cleft palate
 B : Left-sided unilateral complete cleft lip and palate
 C : Bilateral complete cleft lip and palate
 D : Bilateral right incomplete, left complete cleft lip and primary palate

- Extracellular matrix: during the normal merging process, the disappearance of the midline epithelial seam is accompanied by an increase in both proteoglycans (PG) and collagen expression. Control of ECM metabolism in the embryonic oral facial region, therefore, appears to be essential for normal palatal development. ECM molecules in turn promote the activities of growth factors and cytokines present in the epithelial cell and palatal mesenchyme.
 - Although, the role of B-cell leukemia/lymphoma 3 (BCL3) in the etiology of CLP is unknown, proto-oncogene BCL3 is related to genes involved in cell lineage determination and cell cycle regulation.
 - Retinoic acid receptors (RAR): The region on chromosome 11 associated with CLP in this animal model is homologous to 17q21 - q24 in humans.²³ This region, marked by retinoic acid receptor a (RAR) has shown association with CLP in some populations.²⁴ This study has strengthened the case for CLP locus linked to RAR in humans.
 - Chromosome 6: Chromosome 6 has been of interest to investigators because of the association of alleles at the H2 locus with corticosteroid induced clefting in the mouse. HLA (on chromosome 6p) is the human homologue of H2.
 - Chromosome 2
 - Chromosome 19
 - Chromosome 4
 - Chromosome 17
- } also implicated in formation of cleft lip and/or palate
- Environmental factors: Naturally occurring folates are found widely in foodstuffs, especially in liver, legumes and fresh vegetables. Folic acid (pteroylmonoglutamic acid) is a commercially available compound used for supplementation. It does not occur naturally in living tissues, but is readily converted *in vivo* into the biologically active folates. Folate is essential in the synthesis of purines and pyrimidines, which are components of DNA and RNA required in the regulation of gene expression and cell differentiation. In humans, drugs that interfere with folate metabolism, e.g. phenytoin, are known to have teratogenic effects. Low blood folate levels were associated with spontaneous abortion and developmental abnormalities of the fetus.²⁵ However, studies have found significant protective effects of the role of folic acid in orofacial clefting.
 - There also appears to be an association between maternal smoking and oral clefting.²⁶
 - Deficiency of vitamins B₁, B₂ and B₆ in the NMRI strain led to embryoletality, teratogenicity and growth retardation among the fetuses. The cleft palate rate was eight times higher in the deficient group than in the control group.

TABLE 1.2: Some syndromes associated with cleft lip and/or palate (+ = present, – = absent)

Syndrome	Cleft Lip	Cleft Palate
Stickler syndrome	–	+
Treacher-Collins	–	+
van der Woude syndrome	+	+
Pierre Robin syndrome	–	+
Ectodermal dysplasia syndrome	+	+
Saethre Chotzen syndrome	–	+
Pallister Hall syndrome	–	+
Waardenburg syndrome	+	+
Basal cell nevus syndrome	+	+
Pfeiffer syndrome	–	+
Holoprosencephaly	+	+
Retinoblastoma	–	+
Shprintzen Goldberg syndrome	–	+
Marfan's syndrome	–	+ (or bifid uvula)
Velocardiofacial	–	+
DiGeorge syndrome	+	+
Apert syndrome	–	+
Crouzon craniofacial dysostosis	–	+
Cleidocranial	–	+
Langer Giedion syndrome	–	+
CHARGE syndrome	+	+

Genetic Basis of Syndromic Cleft Lip and/or Palate

Syndromic cleft lip and/or palate is seen associated with variety of syndromes which present myriad genetic pictures (Table 1.2). Discussion of the genetic make-up of a few of the common craniofacial syndromes has been dealt with in the chapter on bone pathologies. Both syndromic and nonsyndromic cleft lip and/or palate may be associated with other birth defects that are elaborated in Table 1.3.

Prenatal Diagnosis

Ultrasound scanning: For cleft lip, with or without cleft palate, fetal ultrasound studies are the only commonly used test available for prenatal diagnosis (Figs 1.9 and 1.10).

Prenatal Counseling

When the growing fetus in the womb has been identified as having a cleft, the parents will have to go through the process of adjustment in an atmosphere of uncertainty. They will not know exactly what their baby will look like and struggle to cope with images of a fantasized imperfect child. There are often conflicting images of the anticipated child like the concept of a chubby wholeness vies with the unknown. After the genetic evaluation is completed, it is time to sit with the family for genetic counseling. This is usually the longest part of the genetic evaluation, because it is necessary to educate the family regarding issues of heredity and development. The principles of good prenatal counseling are:

TABLE 1.3: Other birth defects associated with cleft lip and/or cleft palate

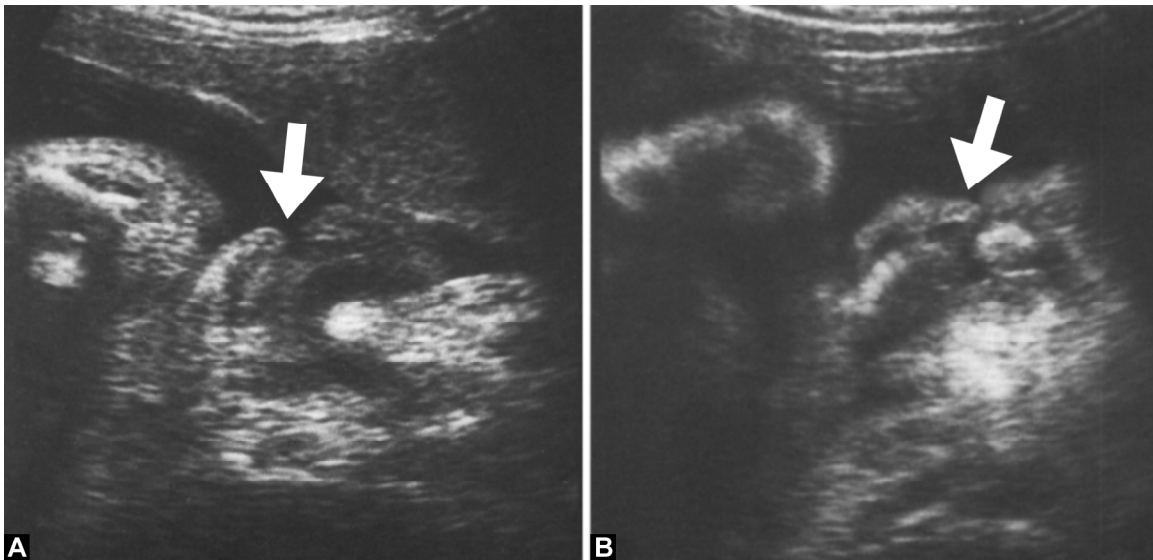
System	Specific findings
Facial malformations	• Hypertelorism • Facial asymmetry • Hemangiomas • Choanal atresia • Microstomia • Low-set ears • Auricular malformations • Preauricular skin tags • Ear canal atresia
Cardiac system	• Ventricular septal defects • Transposition of the great vessels • Patent ductus arteriosus • Tetralogy of Fallot • Total anomalous pulmonary venous return • Single ventricle • Peripheral pulmonary artery stenosis
Gastrointestinal system	• Pyloric stenosis • Esophageal atresia • Anal fistula • Inguinal hernia • Diaphragmatic hernia
Central nervous system	• Visual impairment • Problems with balance • Hydrocephalus • Holoprosencephaly • Seizures
Musculoskeletal system	• Lumbar spine kyphosis • Vertebral and costal deformities

NOTE: These defects can also occur as isolated abnormalities and do not always indicate that the infant has cleft lip and/or cleft palate. A physical assessment must always involve a thorough examination of facial features, including the lip and palate, to rule out cleft lip and/or palate regardless of other findings on examination.

1. Parents should be given accurate information by someone with experience in clefts.
2. The time from diagnosis to support should be as brief as possible.
3. Parents should have early contact with members of the cleft team.
4. All members of the family should be given the opportunity to express their concerns and their emotional responses.
5. They should all be helped to prepare for the birth by having a clear view of how the baby is likely to look.
6. Any discussion of termination should begin with the parents on the basis of accurate information.²⁷

Perinatal Counseling

It is important that parents receive experienced counseling when the baby is born. This helps parents feel less alone even though it is not a substitute for skilled professional care.



FIGURES 1.9A and B: Cleft lip and palate at 38 weeks showing the two common ultrasound orientations to detect clefting. Left image is axial through the lip and shows a cleft (arrow). Right image is coronal through the tip of the nose, lips and chin. Note the cleft (arrow) which extends into and deforms the nostril (complete cleft lip)



FIGURE 1.10: Bilateral complete cleft lip/palate (small arrows) with the premaxilla protruding anteriorly as a mass (open arrow)—Axial view through fetal lip at 25 weeks

The principles of good perinatal counseling are:

1. All families should have access to experienced counseling.
2. Early assessment of problems is important.
3. The needs of all family members should be recognized.
4. Strengths should be emphasized rather than weaknesses.
5. Parents should be empowered to gain mastery through interaction with professionals and access to relevant information.²⁸

Postnatal Counseling

Some parents do have great difficulty adjusting to the cleft and find it becomes difficult to accept their child. This may be expressed as emotional distancing from the baby, but it may also be expressed as a defensive overprotectiveness as the parent strives to cope with negative feelings and a sense of personal incompetence. Problems with adjustment may be masked by the physical needs of the new baby and whilst the distraught mother is easy to identify and help, it is not so easy to recognize the angry or depressed mother, nor the one who withdraws into an introspective depressive state.

Principles of good postnatal counseling are:

1. Individual needs should be assessed in a non-judgmental way.
2. Communication should be encouraged between family members.
3. Social and family support should be mobilized where it is lacking.
4. If necessary, other agencies should be contacted to help deal with particular problems.
5. Long-term dependency on the counselor should be avoided and normalization of family life should be encouraged.

Children can learn to live with a disability. But they cannot live well without the conviction that their parents find them utterly lovable. If the parents, knowing his defect, love him now, he can believe that others will love him in the future. With this conviction he can live well now and have faith in the years to come.²⁹

Policy on Management of Patients with Cleft Lip/Palate and Other Craniofacial Anomalies

The American Academy of Pediatric Dentistry (AAPD), in its efforts to promote optimal health for children with cleft lip/palate and other craniofacial anomalies, endorses the current statements of the American Cleft Palate-Craniofacial Association (ACPA).

Several fundamental principles were identified as critical to optimal cleft/craniofacial care. These principles are:

1. Management of patients with craniofacial anomalies is best provided by an interdisciplinary team of specialists.
2. Optimal care for patients with craniofacial anomalies is provided by teams that see sufficient numbers of these patients each year to maintain clinical expertise in diagnosis and treatment.
3. Although referral for team evaluation and management is appropriate for patients of any age, the optimal time for the first evaluation is within the first few weeks of life and whenever possible, within the first few days.
4. From the time of first contact with the child and family, every effort must be made to assist the family in adjusting to the birth of a child with a craniofacial anomaly and the consequent demands and stress placed upon that family.
5. Parents/caregivers must be given information about recommended treatment procedures, options, risk factors, benefits and costs to assist them in
 - a. Making informed decisions on the child's behalf
 - b. Preparing the child and themselves for all recommended procedures

The team should actively solicit family participation and collaboration in treatment planning and, when the child is mature enough to do so, he or she should also participate in treatment decisions.

6. Treatment plans should be developed and implemented on the basis of team recommendations.
7. Care should be coordinated by the team, but should be provided at the local level whenever possible; however, complex diagnostic or surgical procedures should be restricted to major centers with appropriate treatment facilities and experienced care providers.
8. It is the responsibility of each team to be sensitive to linguistic, cultural, ethnic, psychosocial, economic and physical factors that affect the dynamic relationship between the team, patient and family.
9. It is the responsibility of the team to monitor both short-term and long-term outcomes. Thus, longitudinal follow-up of patients, including appropriate documentation and record keeping, is essential.

10. Evaluation of treatment outcomes must take into account the satisfaction and psychosocial well-being of the patient, as well as effects on growth, function and appearance.

As members of the interdisciplinary team of physicians, dentists, speech pathologists and other allied health professionals, pediatric dentists should provide dental services in close cooperation with their orthodontic, oral and maxillo-facial surgery and prosthodontic colleagues.

All dental specialists should ensure that:

1. Dental radiographs, cephalometric radiographs and other imaging modalities as indicated should be utilized to evaluate and monitor dental and facial growth and development.
2. Diagnostic records, including properly occluded dental study models, should be collected at appropriate intervals for patients at risk for developing malocclusion or maxillary-mandibular discrepancies.
3. Presurgical maxillary orthopedics to improve the position of the maxillary alveolar segments prior to surgical closure of the lip may be indicated for some infants.
4. As the primary dentition erupts, the team evaluation should include a dental examination and if such services are not already being provided, referral to appropriate providers for caries control, preventive measures and space management.
5. Before the primary dentition has completed eruption, the skeletal and dental components should be evaluated to determine if a malocclusion is present or developing.
6. Depending upon the specific goals to be accomplished and also upon the age at which the patient is initially evaluated, orthodontic management of the malocclusion may be performed in the primary, mixed or permanent dentition. In some cases, orthodontic treatment may be necessary in all 3 stages.
7. While continuous active orthodontic treatment from early mixed dentition to permanent dentition should be avoided, each stage of orthodontic therapy may be followed by retention and regular observation. Orthodontic retention for the permanent dentition may extend into adulthood.
8. For some patients with craniofacial anomalies, functional orthodontic appliances may be indicated.
9. For patients with craniofacial anomalies, orthodontic treatment may be needed in conjunction with surgical correction of the facial deformity.
10. Congenitally missing teeth may be replaced with a removable appliance, fixed restorative bridgework, or osseointegrated implants.

11. Patients should be closely monitored for dental and periodontal disease.
12. Prosthetic obturation of palatal fistulae may be necessary in some patients.
13. A prosthetic speech device may be used to treat velopharyngeal inadequacy in some patients.³⁰

Role of the Pedodontist in Management of Cleft Lip and Palate

The complete rehabilitation of this condition definitely requires a multidisciplinary approach involving a pediatrician, oral surgeon, plastic surgeon, prosthodontist, dietician, speech therapist, with the pedodontist providing an invaluable input.

Early dental management of cleft lip and palate includes:

1. Intraoral maxillary obturator therapy
2. Appliance for premaxillary retractions
3. Management of dental problems

Intraoral maxillary obturator: Feeding problems are often associated with infants affected with cleft lip and palate, making it difficult to maintain adequate nutrition.

These problems include:

- Insufficient suction to pull milk from the nipple
- Excessive air intake during feeding
- Choking
- Nasal regurgitation
- Excessive time required for nourishment

Special nipples and bottles are available that create an easy flow. Feeding equipment includes bottles, teats, cups, spoons, NUK orthodontic nipple, Mead Johnson squeezable cleft palate feeder, the Haberman feeder. Feeding techniques (e.g. Richard's 1991 Enlargement, Stimulate, Swallow, Rest [ESSR] method), breast-feeding, prostheses, and nutrition/lactation advice also assist in the feeding routine of the child. A soft bottle can be squeezed gently during feeding to let the baby get enough formula.

The intraoral maxillary obturator proves beneficial by providing an artificial palate.

Advantages of this are:

- It reduces feeding difficulties and helps to maintain adequate nutrition.
- It provides maxillary cross arch stability; prevents arch collapse after cheiloplasty.
- It helps maxillary orthopedic moulding of the cleft segments into approximation before primary alveolar cleft bone grafting.

This appliance is most useful during 0-3 months period, until the time of initial lip closure.

Appliances for premaxillary orthopedics (birth-4 to 5 months)

In cases of bilateral cleft lip and palate, the premaxillary segment is either placed severely anterior to the maxillary arch

or divided laterally to one side of the cleft. In such cases, lip surgery becomes difficult if anteroposterior and vertical repositioning of the premaxilla is not carried out. After the delivery of the obturator, one week later (period of adjustment), the infant is fitted with a premaxillary retraction appliance.

This could be:

- Premaxillary retraction strap with a baby bonnet made to provide "headgear anchorage". Bonnet and strap appliance to be worn 24 hours a day, removed only during feeding, for 6 to 8 weeks.
- In case of laterally deviated premaxilla with bilateral cleft lip and palate, an external acrylic bulb prosthesis is anchored to the infant's head with a bonnet appliance.

Cheiloplasty (surgical lip closure): A general "rule of tens" is used in determining optimal timing of lip closure, i.e. 10 weeks of age, 10 pounds of body weight, 10 gms Hb. At the time of lip closure, when the infant is under general anesthesia, an impression is made for the new obturator.

Maxillary orthopedics: Between the 3rd and 9th month of age, to prevent collapse of maxillary arches, the obturator is used to provide cross arch stability and support. As pressure is exerted on anterior segments of maxilla by the repaired lip, orthopedic molding of the segments can be achieved. This is facilitated by the obturator.

Closure of palatal cleft by bone grafting: Following are the bone grafting procedures that are well accepted by the practitioners:

- Primary bone grafting—Less than two years of age
- Early secondary bone grafting—Two to four years of age
- Secondary bone grafting—Six to fifteen years of age
- Late secondary bone grafting—In adults (residual alveolar cleft reconstruction).

Management of dental problems

This includes:

- Establishment and maintenance of optimum oral health
- Prevention of decay in the teeth adjacent to the cleft (as these areas favor food lodgement)
- Correction of ectopically erupted teeth and crossbite
- Interceptive correction of traumatic occlusions
- Maxillary expansion - routine palatal expansion (especially in patients who have not undergone primary cleft bone grafting)
- Orthodontic treatment for alignment and occlusion.³¹

The treatment protocol can be more conveniently delineated according to the type of dentition as follows:

Primary dentition treatment: At this age, a proper alignment and/or expansion of the primary dentition can be done more easily. But, often the problems are not very severe at this stage and does not require a very active or enthusiastic

treatment. Simple forms of a fixed maxillary lingual appliance are preferred over the removable split palatal type of appliance because of occasional cooperation problems and a high relapse rate with a removable appliance. In a few cases, speech pathologists advise palatal expansion for improving speech.

Mixed dentition treatment: Some problems requiring attention at this stage are:

1. **Minor crossbites:** Crossbites may be corrected by expansion by usual methods. Once correction is complete, full time retention is required. This is because there is no midpalatal suture system to fill in bone and consolidate the expanded maxillary segments. Even if the crossbite is corrected and a retention device given at this stage, the possibility of a need to re-expand at the permanent dentition stage cannot be ruled out. This is because of aggravated maxillary hypoplasia with growth.
2. **Retroclination of permanent incisors and anterior cross-bite:** May lead to esthetic, speech and psychological problems. To correct this usually a partial banded approach is needed. Once alignment is corrected, a full time retention device is needed.
3. **Crowded dentition:** This may require serial extraction whereby primary cuspids are removed to treat incisor crowding and the primary molars may be removed to hasten the eruption of the first bicuspid.
4. **After alveolar bone grafting:** It is usually done just before the canine erupts. Orthodontic movement of the canine may be initiated 6 weeks following placement of the bone graft. With orthodontic movement of the canine enough space is created in the arch to allow the cuspids to erupt.

Permanent dentition treatment: The principles and techniques of permanent dentition treatment of cleft lip and palate cases are similar to those in non cleft orthodontics, except the period of retention is invariably longer. The main problems at this stage are posterior crossbites and malposed permanent incisors.

If orthognathic surgery is done to correct the underlying skeletal imbalance, preoperative and postoperative orthodontic treatment is a must to achieve proper alignment, position and inclination of the teeth on their respective arches.

The possibility of opening of the oronasal fistula due to arch expansion resulting in increased hypernasality and nasal regurgitation must be discussed before starting orthodontic treatment.

Plastic surgery is one of those fascinating branches of medical science which challenges the very verdict of nature by remodeling the shape of tissue/structure. In other words, plastic surgery can be termed as RECREATION. It gives an opportunity to the individual to RELIVE. In the context of our country, one can even say that the effects of plastic surgery are akin to REINCARNATION and allow a person to live a

new life of dignity. Nothing short of a miracle for the hapless patient!!!

Preventive measures, per se, are still a distant hope in the legend of cleft lip and palate; yet with so many organizations and research centers working towards unraveling the genetic basis of cleft lip and palate, we can be hopeful of a day when we would be able to prevent this condition altogether.

CHEILITIS GLANDULARIS

Von Volkman, 1870,³⁷ coined the term cheilitis glandularis and described it as a chronic inflammatory condition of the lower lip characterized by mucopurulent exudates from the ductal orifices of the labial minor salivary glands. It is a chronic progressive and uncommon inflammatory condition of the minor salivary glands.

Etiology

- May be a manifestation of chronic irritation.
- Factitial trauma, excessive wetting of lips by frequent licking.
- May be associated with mouth breathing and asthma.
- Poor oral hygiene
- Syphilis
- Heredity

Clinical Features

- Usually found on the lower lip. May also involve upper lip and palate.
- Cases have been reported in women and children, but occur most often in middle aged men.
- Eversion of lower lip, inflamed and dilated minor salivary gland ducts, burning sensation at the vermillion border of the lip.
- Sometimes, a mucopurulent exudate is seen.
- According to clinical features seen, it is classified into three types:
 1. Simple type: Multiple painless, papular surface lesions with central umbilication.
 2. Superficial suppurative type (Baelz Disease): Painless indurated swelling of the lip with shallow ulceration and crusting.
 3. Deep suppurative (cheilitis glandularis apostematosa): Deep seated infection with formation of abscesses, sinus tracts and fistulas.

Histopathologic Findings

- Lesional tissue shows inflamed, dilated minor salivary gland ducts (Fig. 1.11).
- In some cases, dysplastic changes may be seen in the overlying surface epithelium.

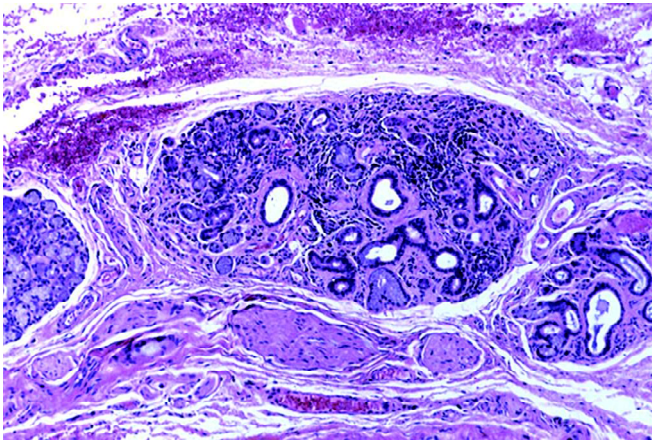


FIGURE 1.11: Histopathologic picture of cheilitis glandularis showing ductal ectasia, acinar atrophy, interstitial fibrosis and inflammation of minor salivary glands

Management

1. Treatment is based on histopathologic findings.
2. Vermillionectomy, if the lesion is associated with actinic damage.

CHEILITIS GRANULOMATOSA

It is a chronic swelling of lip due to granulomatous inflammation.

Etiology

Etiology is unknown; a possibility of genetic predisposition has been implicated. Sometimes contact antigens may play a role.

Clinical Features

- The lesion is seen most commonly in young adults.
- There is no sex predilection.
- Diffuse or nodular episodic swellings on lip or the face and mostly involving upper lip, lower lip, eyelids and one side of the face (Fig. 1.12).
- Initially the lesion is soft but as time progress, it becomes rough, dry, painful and firm in consistency; especially those occurring on the lips.
- Other features include fissured tongue, unilateral or bilateral facial palsy and lymphadenopathy.

Histopathologic Features

- Lesional areas show a central zone of noncaseating granuloma consisting of epithelioid cells and Langhans giant cells (Fig. 1.13).



FIGURE 1.12: Cheilitis granulomatosa showing diffuse episodic swelling on lower lip

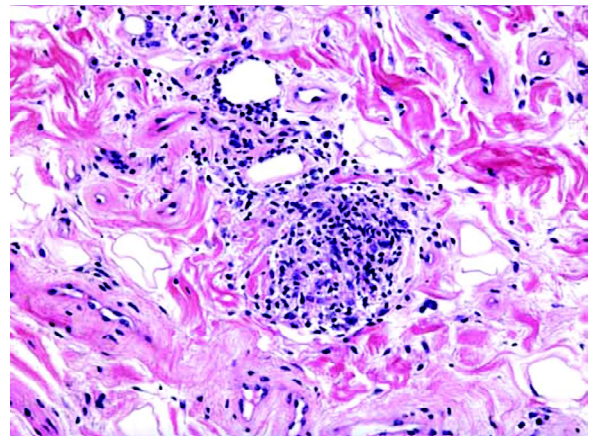


FIGURE 1.13: Histopathologic picture of cheilitis granulomatosa showing a central zone of non-caseating granuloma

- Peri and paravascular aggregates of chronic inflammatory cell infiltrate mostly lymphocytes, plasma cells and histiocytes are seen.

Management

1. Avoidance of contact with known allergen.
2. Intralesional corticosteroid injections.
3. Use of mast cell stabilizers and non-steroidal anti-inflammatory agents.
4. Surgery
5. Radiation

PEUTZ-JEGHER'S SYNDROME

Peutz-Jeghers syndrome is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in

association with mucocutaneous melanocytic macules.^{32,33} Also called as hereditary intestinal polyposis syndrome, intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules.

A 15-fold elevated relative risk of developing cancer exists in this syndrome over that of the general population; cancer primarily is of the GI tract, including the pancreas and luminal organs and of the female and male reproductive tracts and the lung.

Jeghers, McKusick and Katz (1949) are credited with rediscovery and establishment of clinical significance of generalized intestinal polyposis. First described by Peutz in 1921,³⁴ this obscure syndrome produced melanin spots on oral mucous membranes, extraoral labial tissues and fingers. Jeghers et al presented ten cases in which they described syndromes consisting of same signs and symptoms.³⁵

Etiopathogenesis

Goldberg and Goldhaber (1954) believed that inheritance of Peutz-Jeghers syndrome was simple Mendelian dominant and single pleiotrophic gene was believed to be responsible for both melanin spots and polyps. Melanin spots and patches varied from 1 to 5 mm.³⁶

The characteristic pathology of Peutz-Jeghers polyps includes extensive smooth muscle arborization throughout the polyp with the appearance of pseudoinvasion because some of the epithelial cells, usually from benign glands, are surrounded by the smooth muscle.

The cause of Peutz-Jeghers syndrome appears to be a germline mutation of the STK11 (serine threonine kinase 11) gene in most cases, located on band 19p13.3.

Clinical Features

- Peutz-Jeghers syndrome has been described in all races.
- The occurrence of cases in males and females is about equal.
- The average age at diagnosis is 23 years in men and 26 years in women.
- Repeated bouts of abdominal pain in patients younger than 25 years are reported.
- Unexplained intestinal bleeding in a young patient has also been reported.
- Prolapse of tissue from the rectum may be seen. Rectal mass or rectal polyp is seen.
- Menstrual irregularities in females (due to hyperestrogenism from sex cord tumors with annular tubules).
- Precocious puberty may also occur.
- Cutaneous pigmentation (1 to 5 mm macules) of the perioral region crossing the vermillion border (94 %), perinasal and perioral areas is seen (Fig. 1.14).

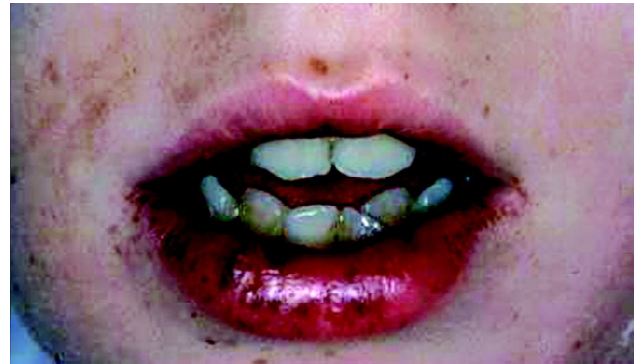


FIGURE 1.14: Peutz-Jegher's syndrome showing cutaneous pigmentation of the perioral region crossing the vermillion border

- Mucous membrane pigmentation, primarily the buccal mucosa (66 %) is seen.
- Pigmentation may be present on the fingers and toes, on the dorsal and velar aspects of the hands and feet, and around the anus and genitalia and may fade after puberty.
- Gynecomastia and growth acceleration (due to Sertoli cell tumor) may be seen.
- Testicular mass may also be present.

Laboratory Findings

A CBC count should be obtained because the polyps may be a source of blood loss.

Histopathologic Findings

Characteristic pathology of Peutz-Jeghers polyps includes extensive smooth muscle arborization throughout the polyp, with the appearance of pseudoinvasion because some of the epithelial cells, usually from benign glands, are surrounded by the smooth muscle.

Management

1. Annual physical examination that includes evaluation of the breasts, abdomen, pelvis and testes
2. Annual complete blood count
3. Repeated removal of hemorrhagic or large polyps (> 5 mm) by endoscopic polypectomy.

LABIAL AND ORAL MELANOTIC MACULE

Oral melanotic macule represents a focal area of melanin deposition, as a result of increase in number of melanocytes, mostly occurring on the buccal mucosa.

Another term **labial melanotic macule** is used to represent an entity similar to oral melanotic macule, occurring on the vermillion border of the lip (Fig. 1.15).



FIGURE 1.15: Labial melanotic macule presenting as a black, round shaped lesion

Clinical Features

- The lesion may be seen occurring at any age.
- Incidence of occurrence is more common in females as compared to males.
- Lesions most commonly occur on lower lip, buccal mucosa, gingiva and palate.
- It occurs as a dark brown to black, round to oval shaped lesion in the oral cavity.

Histopathologic Features

1. Lesional area shows abundant melanin deposits within keratinocytes in the basal and parabasal layer.
2. There is no underlying inflammatory cell infiltrate.

Management

1. No specific treatment.
2. Lesion should be sometimes biopsied to rule out any malignancy.

DEVELOPMENTAL DISTURBANCES OF THE ORAL MUCOSA

- Fordyce's granules
- Focal epithelial hyperplasia

FORDYCE'S GRANULES

This is not a disease of oral mucosa but a developmental anomaly characterized by heterotropic collection of sebaceous glands at various sites in the oral cavity.

Clinical Features

- Fordyce's granules appear as small yellow spots, either discretely separated or forming relatively large plaques, often projecting slightly above the surface of tissue (Fig. 1.16).



FIGURE 1.16: Fordyce's granules appearing as small yellow, discretely separated spots

- They are most frequently found in a bilaterally symmetrical pattern on the buccal mucosa opposite the molar teeth and also on the inner surfaces of lips, in the retromolar region lateral to the anterior faucial pillar and occasionally on tongue, gingiva, frenum and palate.
- Ectopic sebaceous glands have been discussed in a review by Guiducci and Hyman and may occur in oesophagus, uterine cervix, male genitalia, nipples, palms and soles, parotid gland, larynx and orbit.³⁸
- Studies by Halperin and coworkers, confirmed by Miles, have indicated that this oral condition is present in approximately 80 percent of the population.³⁹
- Miles has reported that a large number of sebaceous glands in cheeks and lips may sometimes be found in children long before the age of puberty.⁴⁰

Histopathologic Features

- In a microscopic view of a Fordyce's granule, sebaceous glands are clearly seen (Fig. 1.17).
- Sebaceous glands are found normally in large numbers on the skin where they are associated with hair follicles.
- These sebaceous glands are similar histologically to those seen in skin.
- A single hair follicle and hair shaft growing from gingiva is a rare occurrence and has been reported by Baughman, 1980.⁴¹
- Glands are superficial and may consist of few or many lobules all grouped around one or more ducts which open on the surface of mucosa.
- Ducts may show keratin plugging.

Management

No specific treatment required

Focal Epithelial Hyperplasia

Refer to chapter on epithelial pathology.

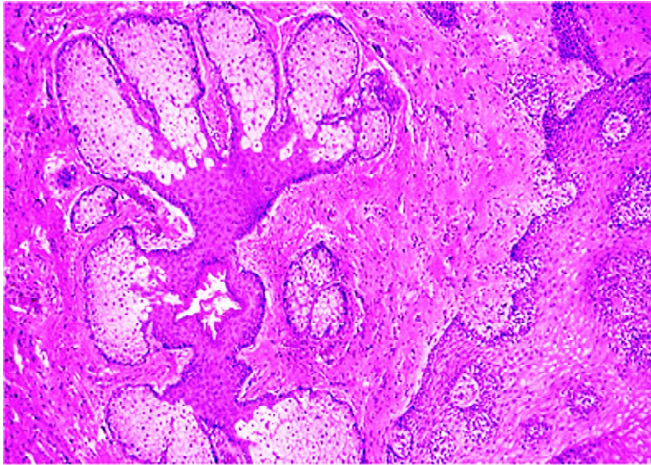


FIGURE 1.17: Histopathologic picture of Fordyce's granules showing superficial sebaceous glands consisting of few or many lobules

DEVELOPMENTAL DISTURBANCES OF THE GINGIVA

- Fibromatosis gingivae
- Retrocuspid papilla

FIBROMATOSIS GINGIVAE

Refer to chapter on gingival and periodontal diseases in the pediatric population.

RETROCUSPID PAPILLA

It is a small papule that most frequently appears bilaterally on the lingual mucosa of mandibular bicuspid. It was first described by Hirshfeld in 1933.⁴²

Clinical Features

- It occurs as a small, well-circumscribed, soft, pink colored papule, bilaterally on mandibular lingual mucosa between free gingival margin and mucogingival junction.
- Incidence of occurrence in children and young adults is between 25 to 99 percent and gradually decreases with increase in age.
- According to Berman and Fay, 1976, the lesion occurs more commonly in males as compared to females.⁴³

Histopathologic Features

- The lesional area reveals vascularized fibrous connective tissue with presence of numerous large stellate fibroblasts containing numerous nuclei.
- The overlying epithelium is atrophic and may show hyperorthokeratosis or parakeratosis.

Management

No specific treatment required

DEVELOPMENTAL DISTURBANCES OF THE TONGUE

- Aglossia and microglossia
- Macroglossia
- Ankyloglossia or tongue tie
- Cleft tongue
- Fissured tongue
- Median rhomboid glossitis
- Benign migratory glossitis
- Hairy tongue
- Lingual varices
- Lingual thyroid nodule.

AGLOSSIA AND MICROGLOSSIA

A very rare anomaly, only 35 cases have been reported in a period spanning 258 years. It is mostly associated with cleft palate and dental agenesis.

Pathogenesis

Unknown, but may be due to lack of muscular stimulus between alveolar arches, which results in retardation of growth of the mandible in an anterior direction.

Clinical Features

- Microglossia is characterized by an abnormally small tongue.
- Even though aglossia indicates the absence of a tongue, there is almost always the presence of a rudimentary small tongue.
- May be associated with oromandibular-limb hypogenesis syndrome. It is characterized by hypodactylia (absence of one or more digits), hypomelia (hypoplasia of part or all of a limb) and microglossia.
- Microglossia is frequently associated with hypoplasia of the mandible and lower incisors may be missing.

Management

1. Depends upon nature and severity of the condition.
2. Surgery may help in improving oral function.
3. Orthodontics may also help in improving esthetics and oral function.

MACROGLOSSIA

The term denotes an enlarged tongue. Macroglossia has been described as far back as the era of Egyptian **Papyrus Ebers** from around 1550 BC (Fig. 1.18).

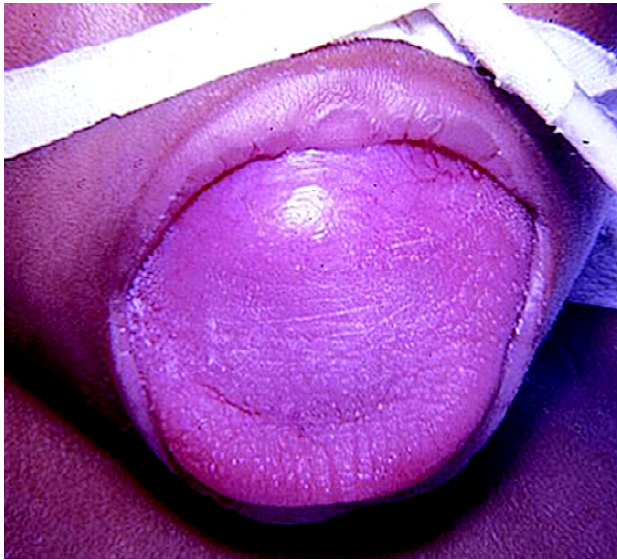


FIGURE 1.18: Macroglossia

Etiology

Etiology of macroglossia

Congenital

- Hemangioma
- Lymphangioma
- Down syndrome
- Beckwith-Wiedemann syndrome
- Lingual thyroid
- Trisomy 22
- Laband syndrome
- Mucopolysaccharidosis
- Multiple endocrine neoplasia Type 2B.

Acquired

Metabolic/Endocrine:

- Hypothyroidism
- Cretinism
- Diabetes.

Inflammatory/Infectious:

- Syphilis
- Amebic dysentery
- Ludwig angina
- Pneumonia
- Rheumatic fever
- Small pox
- Typhoid
- Tuberculosis
- Actinomycosis
- Candidiasis.

Systemic/Medical conditions:

- Hypertrophy
- Neurofibromatosis
- Iatrogenic.

Traumatic:

- Surgery
- Hemorrhage
- Direct trauma
- Intubation injury.

Neoplastic

- Lingual thyroid

Infiltrative

- Amyloidosis
- Sarcoidosis.

Clinical Features

- Commonly occurs in children.
- Ranges from a mild to severe degree.
- In infants, it may be manifested by noisy breathing, drooling and difficulty in eating
- Pressure on tongue against the teeth produce crenated lateral borders to the tongue, open bite and mandibular prognathism
- Tongue may ulcerate, get infected and finally necrosed
- Macroglossia is associated with Beckwith-Wiedemann syndrome characterized by omphalocele (protrusion of part of the intestine through a defect in the abdominal wall at the umbilicus), visceromegaly, gigantism and neonatal hypoglycemia. It follows an autosomal dominant mode of inheritance and carries a high risk of childhood visceral tumors including Wilms tumor, adrenal carcinoma and hepatoblastoma.
- Appearance of the tongue varies with the cause:
 - A diffuse, smooth, generalized enlargement is seen in hypothyroidism
 - A multinodular appearance is seen in amyloidosis, neurofibromatosis and multiple endocrine neoplasia
 - A pebbly surface with multiple vesicle like blebs is seen in lymphangioma
 - A papillary surface is seen in Down syndrome
 - Unilateral enlargement is seen in hemifacial hyperplasia.

Pseudomacroglossia

- Pseudomacroglossia is the term applied to a condition which forces the tongue to sit in an abnormal position. These conditions could be:
 - Habitual posturing of the tongue
 - Enlarged tonsils or adenoids
 - Low palate
 - Transverse, vertical, anterior/posterior deficiency in the maxillary or mandibular arches
 - Severe mandibular retrognathism, neoplasm displacing the tongue, hypotonia of the tongue

Histopathologic Features

- Depends on the specific cause
 - In case of Down syndrome, no histologic abnormality can be detected.
 - In case of a tumor, neoplastic proliferation of a particular tissue may be seen.
 - In case of Beckwith-Wiedemann syndrome, increased muscle tissue is seen.
 - In case of amyloidosis, an abnormal protein material may be seen deposited.

Management

1. In mild cases, no specific treatment is required.
2. In severe conditions, glossectomy is required to improve functions.

ANKYLOGLOSSIA (Fig. 1.19)

It is commonly known as tongue tie. Ankyloglossia occurs when a short lingual frenum attaches to the bottom of the tongue. Mostly occurs in 2 to 3 of every 10,000 people.

Clinical Features

- Occurs as a mild and severe form
- Mild form is of little clinical significance as compared to the severe form in which the tongue is fused to the floor of the mouth
- Occurs in 1.7 to 4.4 percent of neonates
- Follows a male predilection
- May contribute to the development of an anterior open bite.
- Clefting of tongue may be occasionally associated with ankyloglossia
- High mucogingival attachment leads to periodontal problems



FIGURE 1.19: Tongue-tie due to high lingual frenal attachment

- Inability to maintain oral hygiene in the mandibular anteriors
- May result in speech defects
- May be associated with dyspnea due to upward and forward displacement of the epiglottis and larynx.

Management

1. In mild cases, no specific treatment is required.
2. In severe cases, when there are functional or periodontal difficulties, frenectomy is recommended. Surgery is required only if:
 - Speech problems are present
 - Periodontal maintenance of the mandibular anteriors is difficult.
3. In younger children, surgery is postponed until the age of 4 or 5.

CLEFT TONGUE

It is a rare anomaly. Mostly occurs due to lack of emergence of lateral lingual swellings. More commonly seen is a partial cleft of the tongue or a manifestation of a cleft as only a deep groove running along the midline of the dorsal surface.

Etiology

Incomplete merging and failure of groove obliteration by underlying mesenchymal proliferation.

Clinical Features

- Associated with oral-facial-digital syndrome with thick, fibrous bands in the lower anterior mucobuccal fold eliminating the sulcus and with clefting of the hypoplastic mandibular alveolar process.
- Food debris and microorganisms may collect at the base of the cleft and cause irritation.

Management

No specific treatment is required, except for keeping the cleft free of debris and inflammation.

FISSURED TONGUE

It is also called as scrotal tongue and lingual plicata. Fissured tongue is a condition frequently seen in the general population that is characterized by grooves that vary in depth and are noted along the dorsal and lateral aspects of the tongue (Fig. 1.20).

Etiology

Largely unknown, although Eidelman et al, 1976, suspected a polygenic mode of inheritance because the condition is seen clustering in families who are affected.⁴⁴



FIGURE 1.20: Fissured tongue

Clinical Features

- Usually asymptomatic, and the condition is initially noted on routine intraoral examination as an incidental finding.
- Slight male predilection has been seen.
- May be diagnosed initially during childhood, but it is diagnosed more frequently in adulthood. The prominence of the condition appears to increase with increasing age.
- Fissured tongue is also associated with Melkersson-Rosenthal syndrome consisting of a triad of persistent or recurring lip or facial swelling, intermittent seventh (facial) nerve paralysis (Bell palsy) and a fissured tongue.
- Also associated with Down syndrome and benign migratory glossitis (geographic tongue).
- Fissured tongue affects the dorsum and often extends to the lateral borders of the tongue. The depth of the fissures varies but has been noted to be up to 6 mm in diameter.
- When particularly prominent, the fissures or grooves may be interconnected, separating the tongue dorsum into what may appear to be several lobules.

Histologic Features

- A biopsy is rarely performed because of its characteristic diagnostic clinical appearance and little clinical significance.
- However, histologic examination has shown an increase in the thickness of the lamina propria, loss of filiform papillae of the surface mucosa, hyperplasia of the rete pegs, neutrophilic microabscesses within the epithelium and a mixed inflammatory infiltrate in the lamina propria.⁴⁵

Management

No specific treatment is required, except for keeping the cleft free of debris and inflammation by brushing the dorsum of the tongue to eliminate debris that may serve as an irritant.

MEDIAN RHOMBOID GLOSSITIS

Median rhomboid glossitis is a condition characterized by a shiny oval or diamond-shaped elevation, invariably situated on the dorsum of the tongue in the midline immediately in front of the circumvallate papillae (Fig. 1.21).⁴⁶

Clinical Features

- Median rhomboid glossitis presents in the posterior midline of the dorsum of the tongue, just anterior to the V-shaped grouping of the circumvallate papillae.
- The long axis of the rhomboid or oval area of red depapillation is in the anteroposterior direction.
- The erythematous clinical appearance is due primarily to the absence of filiform papillae, rather than to local inflammatory changes, as first suggested in 1914 by Brocq and Pautrier.⁴⁷
- Most cases are not diagnosed until middle age of the affected patient, but the entity is, of course, present in childhood.
- 3:1 male predilection is seen.
- Frequently, irritation occurs by consumption of alcohol, hot drinks or spicy foods.
- When it occurs in adults, it may be caused due to candidiasis. This has prompted a recent shift towards the more appropriate diagnostic term of posterior midline atrophic candidiasis.
- Lesions with atrophic candidiasis are usually more erythematous but some respond with excess keratin production and therefore, show a white surface change.

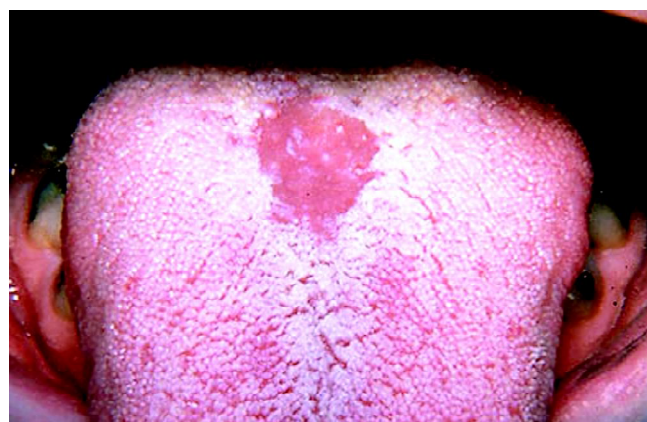


FIGURE 1.21: Median rhomboid glossitis showing erythematous appearance

- Infected cases may also demonstrate a midline soft palate erythema in the area of routine contact with the underlying tongue involvement; this is euphemistically referred to as a **kissing lesion**.
- Lesions are typically less than 2 cm. in greatest dimension and most demonstrate a smooth, flat surface, although it is not unusual for the surface to be lobulated. Occasional lesions have surface mamillations raised more than 5 mm. above the tongue surface, and occasional lesions are located somewhat anterior to the usual location. None have been reported posterior to the circumvallate papillae.

Histopathologic Features

- Median rhomboid glossitis shows a smooth or nodular surface covered by atrophic stratified squamous epithelium overlying a moderately fibrosed stroma with somewhat dilated capillaries.
- Fungiform and filiform papillae are not seen, although surface nodules may mimic or perhaps represent anlage of these structures.
- A mild to moderately intense chronic inflammatory cell infiltrate may be seen within subepithelial and deeper fibrovascular tissues.
- Chronic candida infection may result in excess surface keratin or extreme elongation of rete processes and premature keratin production with individual cells or as epithelial pearls (dyskeratosis) deep in the processes (Fig. 1.22). Silver staining for fungus will often reveal candida hyphae and spores in the superficial layers of the epithelium. This pseudoepitheliomatous hyperplasia may be quite pronounced and the tangential cutting of such a specimen may result in the artifactual appearance of cut rete processes as unconnected islands of squamous epithelium, leading to a mistaken diagnosis of well differentiated squamous cell carcinoma. Because of this

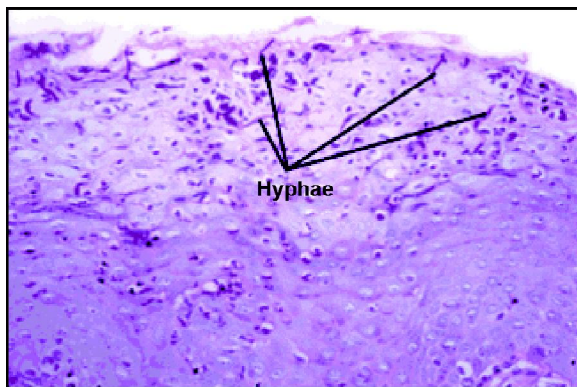


FIGURE 1.22: Candidal hyphae within the superficial layer of the epithelium

difficulty, it is recommended that the patient be treated with topical antifungals prior to biopsy of a suspected median rhomboid glossitis.

Management

1. No treatment is necessary.
2. Nodular cases may be removed and recurrence after removal is generally not noted.
3. Antifungal therapy (topical troches or systemic medication) will reduce clinical erythema and inflammation due to candida infection.

BENIGN MIGRATORY GLOSSITIS (GEOGRAPHIC TONGUE)

An inflammatory disease of the tongue characterized by multiple annular areas of desquamation of the filiform papillae, presenting as reddish lesions outlined in yellow that shift from area to area every few days.

Etiology

- It has been reported with increased frequency in patients with psoriasis and in patients with fissured tongue.
- Although the etiology is unknown, associations with human leukocyte antigen (HLA)-DR5, HLA-DRW6 and HLA-CW6 have been reported.⁴⁸

Clinical Features

- The lesion shows female predilection, which may be related to hormonal factors.
- It is more predominant in adults than in children.
- The tongue exhibits a well-demarcated area of erythema, primarily affecting the dorsum, and often extending to involve the lateral borders of the tongue (Fig. 1.23).
- Within the area of erythema, the normal tongue architecture is effaced, with loss of the filiform papillae and atrophy of the overlying mucosa.
- Surrounding this area of erythema is a well-defined, hyperkeratotic, yellow-white border with an irregular serpiginous outline.

Histopathologic Features

- Lesional area shows a lining of keratinized, stratified squamous epithelium with thin and elongated rete ridges.
- Epithelial area also shows spongiosis and acanthosis. Sometimes, there occurs presence of neutrophils within the epithelium leading to formation of multiple abscesses (**Munro abscesses**).



FIGURE 1.23: Benign migratory glossitis showing depapillation in some areas of tongue

- Connective tissue shows presence of neutrophils and lymphocytes.
- Presence of neutrophilic infiltrate may be responsible for destruction of superficial portion of epithelium producing atrophic and reddened mucosa.

Management

No medical intervention is required because the lesion is benign and most often asymptomatic.

HAIRY TONGUE

Hairy tongue is a common condition of defective desquamation of the filiform papillae, characterized by marked accumulation of keratin on the filiform papillae of the dorsal tongue. It is also called as lingua nigra, lingua villosa nigra and black hairy tongue. It is uncommonly seen in children.

Etiology

Uncertain, but the following associated factors are seen:

- Antibiotic therapy
- Poor oral hygiene
- General debilitation
- Radiation therapy
- Use of oxidizing mouthwashes or antacids
- Overgrowth of fungal or bacterial organisms.

Clinical Features

- Usually appears in the midline, just anterior to the circumvallate papillae, sparing the lateral and anterior borders.

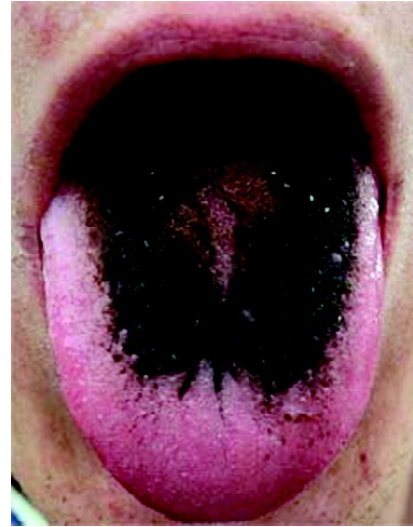


FIGURE 1.24: Black hairy tongue showing black appearance

- Papillae may appear brown, black or yellow depending on growth of pigment producing bacteria and staining of food (Fig. 1.24).
- Tongue appears thick and matted and may occasionally involve the entire dorsal surface.
- Asymptomatic, but occasionally patients may complain of a gagging sensation due to irritation from the elongated papillae or also of a foul taste in the mouth.
- Overgrowth of *candida albicans* may result in glossopyrosis (burning tongue).
- Clinically and etiologically distinct from hairy leukoplakia.

Histopathologic Features

- Diagnosis is usually clinical and since the lesion is asymptomatic, biopsy is rarely performed.
- However, on histopathologic examination, marked elongation and hyperparakeratosis of the filiform papillae is seen (Fig. 1.25).

Management

1. No treatment is necessary as it is a benign, asymptomatic condition.
2. Esthetic appearance of the tongue may be improved with excellent oral hygiene measures.
3. Desquamation of the hyperkeratotic papillae may be encouraged by periodic scraping or brushing with a toothbrush or tongue scraper.
4. Keratolytic agents like podophyllin have been used with variable success, but are not widely recommended in children.

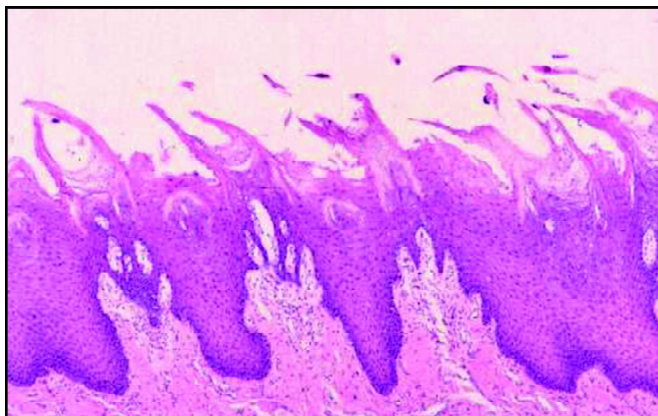


FIGURE 1.25: Histopathologic picture of black hairy tongue showing elongation and hyperparakeratosis of the filiform papillae

LINGUAL VARICES

Lingual varices usually involve the lingual ranine veins appearing as red or purple shot like clusters of vessels on the ventral surface and lateral borders of the tongue as well as in the floor of the mouth (A varix is a dilated, tortuous vein, most commonly subjected to increased hydrostatic pressure but poorly supported by surrounding tissue). Usually appear on the ventral surface of the tongue and floor of the mouth, but may also occur on the upper and lower lip, buccal mucosa and buccal commissure. Generally considered an age related disease and rarely seen in the pediatric age group.

LINGUAL THYROID NODULE (Fig. 1.26)

Lingual thyroid nodule is nothing but ectopic thyroid tissue usually found between foramen caecum and epiglottis. In fact, 90 percent of all ectopic thyroids are found in this region.

Etiopathogenesis

Thyroid gland begins as an epithelial proliferation in the floor of the pharyngeal gut during the 4-5th week of intrauterine life. By the seventh embryonic week, this thyroid bud normally descends into the neck to its final resting position anterior to the trachea and larynx. If the primitive gland does not descend normally, ectopic thyroid tissue may be found between foramen caecum and epiglottis.

Clinical Features

- More frequent in females, probably due to hormonal influences.
- Symptoms may develop during puberty, adolescence, pregnancy or menopause resulting in large nodular masses which may block the airway, causing dyspnea, dysphagia, dysphonia.

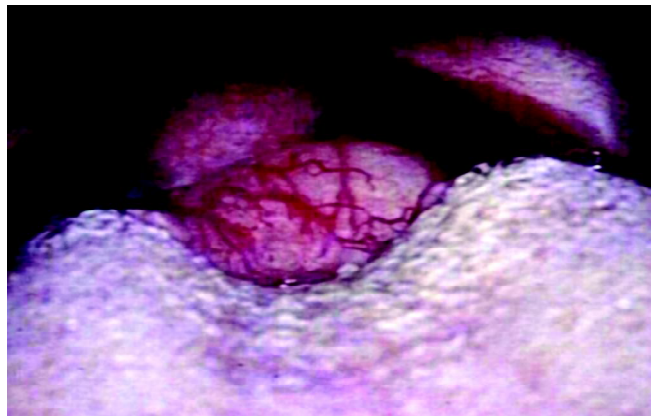


FIGURE 1.26: Lingual thyroid nodule presenting as a large nodular mass on the posterior surface of the tongue

- Seventy five percent of patients with infantile hypothyroidism have some ectopic thyroid tissue which may enlarge as a secondary phenomenon, compensating for thyroid hypofunction.

Diagnosis

- Thyroid scan using iodine isotopes or technetium 99 m.
- Computed tomography and magnetic resonance imaging help in delineating the size and extent of the lesion.
- Biopsy is avoided due to risk of hemorrhage and also as it may be the patient's only thyroid tissue.
- Incisional biopsy may be occasionally required in the adult age group, to rule out malignant changes.

Histopathologic Features

- The lesion shows multiple large pieces of thyroid tissue with thyroid follicles of varying size and shape, lined by uniform cuboidal cells and filled with colloid (Fig. 1.27).
- Some follicles show cystic macrophages in the lumen.

Management

1. No treatment is necessary, except for periodic follow-up in asymptomatic patients.
2. Suppressive therapy with supplemental thyroid hormone is usually recommended in symptomatic patients.
3. If hormone therapy does not help, surgical removal or ablation with radioactive iodine-131 can be performed.
4. Autotransplantation of the surgically excised mass to another body site can be attempted to maintain functional thyroid tissue and to prevent hypothyroidism.

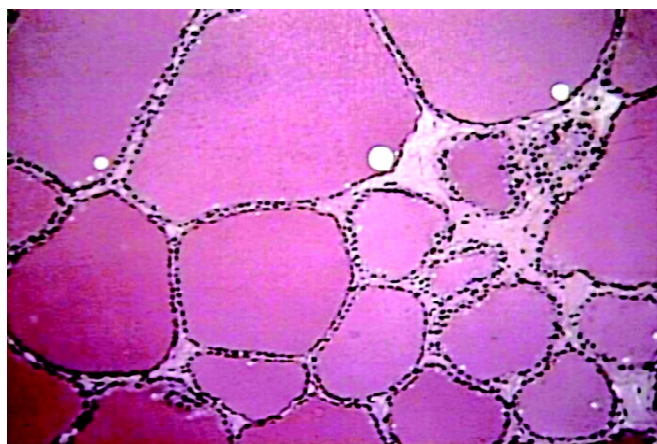


FIGURE 1.27: Histopathologic picture of a lingual thyroid nodule showing thyroid tissue with thyroid follicles

DEVELOPMENTAL DISTURBANCES OF ORAL LYMPHOID TISSUE

- Reactive lymphoid aggregate
- Lymphoid hamartoma
- Angiolymphoid hyperplasia with eosinophilia: This condition is rare in pediatric population and hence does not warrant consideration here.
- Lymphoepithelial cyst: Refer to the chapter on cysts in children.

REACTIVE LYMPHOID AGGREGATE

The lingual tonsil located on the dorsolateral aspect of posterior portion of the tongue frequently becomes inflamed and enlarged. Such an enlargement may be unilateral or bilateral and has been often referred to as 'foliate papillitis'. Similar reactive hyperplasia may be seen as a firm, nodular, tender mass on the buccal mucosa. Sometimes, lymphoid polyps may be seen on the gingival, buccal mucosa, tongue and floor of the mouth.

LYMPHOID HAMARTOMA

It is also called as '**Castleman tumour**'. It is a rare disorder occurring in chest, stomach, neck, armpit, pelvis and pancreas. An abnormal enlargement of lymph nodes in the form of masses is seen in the above locations.

Etiology

The cause of Castleman's disease is unknown, but some researchers have implicated the role of increased production of interleukin-6 (IL-6).

Types

There are two types of Castleman's disease:

1. Hyaline-vascular type
2. Plasma cell type

In hyaline-vascular type, there occur non cancerous growths in lymph nodes and there are no associated symptoms.

Plasma cell type is characterized by fever, weight loss, skin rash, early destruction of red blood cells and hypergamma-globulinemia.

A third form termed as multicentric Castleman's disease has also been described which is characterized by hepato-splenomegaly.

DEVELOPMENTAL DISTURBANCES OF THE SALIVARY GLANDS

This section has been discussed in detail in the chapter on salivary gland diseases in children.

- Aplasia
- Xerostomia
- Hyperplasia of palatal glands
- Atresia
- Aberrancy
- Developmental lingual mandibular salivary gland depression
- Anterior lingual depression.

DEVELOPMENTAL DISTURBANCES AFFECTING THE TEETH

They may be further divided as:

DEVELOPMENTAL DEFECTS IN SIZE OF TEETH

Tooth size varies among different races and the sexes. The sizes are mostly influenced by hereditary, genetic and environmental factors.

- Microdontia
- Macrodontia

MICRODONTIA

It is the term implied for unusually small teeth. They are of two types: True and Relative. True form is applied to the teeth that are physically smaller. Sometimes, normal dentition appears small due to presence of large jaws and then the term relative microdontia is applied.

Clinical Features

- It is most commonly associated with hypodontia.
- It shows a female predilection.
- Most commonly seen in maxillary lateral teeth, called as 'peg laterals'. This appears as a reduction in mesiodistal dimension and convergence towards the incisal edges.
- This condition occurs as an autosomal dominant trait with prevalence in 0.8 to 8.4 percent individuals.
- Generalized microdontia occurs in Down syndrome and in pituitary dwarfism (Fig. 1.28).



FIGURE 1.28: Generalized microdontia showing interdental spacing



FIGURE 1.29: Macrodontia

Management

1. Cosmetic recontouring or veneering of a localized hypodont tooth may be done to improve esthetics.
2. In case of peg laterals, full porcelain crowns are recommended.

MACRODONTIA (FIG. 1.29)

Opposite of microdontia, it is the term applied to unusual large-sized teeth. They are of two types: True and Relative. True form is applied to the teeth that are physically larger. Sometimes, normal dentition appears large due to crowding or due to presence of smaller jaws and then the term relative macrodontia is applied.

Clinical Features

- It is most often seen associated with hyperdontia.
- It occurs more commonly in males as compared to females.
- Diffuse macrodontia is seen in pituitary gigantism and pineal hyperplasia with hyperinsulinism.

Management

No specific treatment required.

DEVELOPMENTAL DEFECTS IN SHAPE OF TEETH

- Gemination
- Fusion
- Concrescence
- Dilaceration
- Talon's cusp
- Dens in dente
- Dens evaginatus
- Taurodontism
- Supernumerary roots

GEMINATION (Fig. 1.30)

Initially the term gemination was used for a tooth with a bifid crown and a common root and root canal as a result of a single tooth bud dividing into two. There was a lot of controversy over this definition, as most of the investigators objected over a joining of two teeth in case of maxillary central incisor or joining of maxillary central incisor with a mesiodens to be counted as a single tooth as for then, the tooth number would be correct.

As far as current concepts are concerned, gemination is defined as a single enlarged tooth or joined tooth in which the tooth count is normal, when the anomalous tooth is counted as one.

Clinical Features

- Occurs in both primary and permanent dentitions.
- Prevalence is 0.5 percent in deciduous teeth and 0.1 percent in permanent dentition.
- Most commonly seen in maxillary anterior region.
- Geminated teeth show the presence of a single root canal.



FIGURE 1.30: Gemination seen in maxillary central incisors



FIGURE 1.31: Fusion of left maxillary central and lateral incisors

Management

1. In deciduous dentition, if there is presence of crowding, spacing and delayed or ectopic eruption of underlying permanent teeth, extraction of the involved tooth is recommended.
2. Surgical division with endodontic therapy of a permanent tooth may be performed to improve esthetics.

FUSION (FIG. 1.31)

Initially fusion was considered as the union of two normally separated tooth buds with the resultant formation of a joint tooth with confluence of dentin. The current concept defines fusion as a single enlarged tooth or joined tooth in which the tooth count reveals a missing tooth when the anomalous tooth is counted as one.

Clinical Features

- Occurs in both primary and permanent dentitions.
- Most commonly seen in maxillary anterior region.
- It is difficult to differentiate between gemination and fusion, but mostly separate root canals are seen in case of fused teeth.
- Most common occurrence is unilateral, but also occasionally bilaterally seen with the prevalence of 0.02 percent.

Management

1. In deciduous dentition, if there is presence of crowding, spacing and delayed or ectopic eruption of underlying permanent teeth, extraction of the involved teeth is recommended.
2. Surgical division with endodontic therapy of a permanent tooth may be performed to improve esthetics.

CONCRESCENCE

Concrescence was defined as the union of two teeth by cementum without confluence of dentin. The same definition holds true in recent concepts.

Etiopathogenesis

It may be developmental or inflammatory. Developmental union occurs when two teeth in close proximity fuse at the cementum. Inflammatory union occurs when inflammatory changes at the apical portion of the root of either of the teeth may resolve by fusion of the apices of the two teeth at the cementum.

Clinical Features

- Most commonly seen in the maxillary posterior region.
- Developmental pattern mostly involves second molar tooth in which its roots are closely placed with the adjacent impacted third molar.
- Post inflammatory pattern is seen in carious molars in which apices of the roots lie closely to the horizontal or distally angulated third molars.
- Post inflammatory concrescence must be kept in mind whenever extraction is planned for nonvital teeth with apices that overlie the roots of an adjacent tooth.

Management

1. If union interferes with eruption, surgical removal is recommended.
2. Extraction difficulties may be experienced on attempted removal of a tooth that is unexpectedly joined to its neighbor.

DILACERATION

Dilaceration is an abnormal angulation or bend in the root or crown of a tooth.

Etiopathogenesis

It may arise from an injury that displaces the calcified portion of the tooth germ and remainder of the tooth is formed at an abnormal angle. The bend may also develop due to presence of an adjacent cyst, tumor or odontogenic hamartoma.

Clinical Features

- It occurs most commonly in permanent maxillary incisors followed by mandibular anterior teeth.
- Deciduous teeth may be involved due to injury during neonatal laryngoscopy and endotracheal intubation.
- Abnormal angulation may be present anywhere along the length of the tooth (Fig. 1.32).



FIGURE 1.32: Dilaceration of the root of maxillary central incisor

- Age of the patient and the direction and degree of force appear to determine the extent of the tooth's malformation.
- Affected anterior maxillary teeth fail to erupt in the oral cavity as compared to mandibular anterior teeth.
- Most of the mandibular anterior teeth erupt in the labial or lingual direction and may be non-vital.

Management

1. Extraction is necessary when the involved tooth prevents eruption of its successor.
2. Root dilaceration affects the tooth if it is used as an abutment due to concentration of the stresses abnormally. It can be prevented by splinting the dilacerated tooth to the adjacent tooth.

TALON'S CUSP (FIG. 1.33)

Talon's cusp is an extra cusp present on the lingual surface of the anterior teeth, extending from the cemento-enamel junction to the incisal edge. It appears as a three pronged pattern resembling an Eagle's Talon, hence the name.

Clinical Features

- Incidence of occurrence ranges from 1 to 8 percent.
- It shows no sex predilection.
- It may occur unilaterally or bilaterally.
- Mostly affects permanent maxillary lateral incisors, followed by maxillary central incisors, mandibular incisors and maxillary canines.
- It is rarely seen in children and mostly occurs on maxillary central incisors.
- A developmental groove is seen in the area where the cusp fuses with the involved tooth.



FIGURE 1.33: Talon's cusp in left maxillary central incisor

- It may be associated with other dental anomalies such as supernumerary teeth, odontomas, impacted teeth, peg shaped lateral incisors, dens invaginatus.
- Syndromes associated with this anomaly are Rubinstein-Taybi syndrome and Sturge-Weber syndrome.

Radiographic Features

On radiographs, the cusp appears overlying the central portion of the crown and includes enamel, dentin and occasionally a pulp horn.

Management

1. Talon's cusp may result in malocclusion, caries, periodontal problems and irritation to the adjacent soft tissue. So to prevent this, one mode of treatment is to remove the cusp. Intentional root canal therapy may be required for the tooth.
2. Periodic grinding of the cusp with application of desensitizing agent such as fluoride varnish is also recommended.
3. If excessive dentin is removed, the cusp is completely ground and then application of calcium hydroxide and placement of composite resin is done.
4. If a developmental groove is left after grinding the cusp, it is restored with restorative materials, or sealed with pit and fissure sealants in order to prevent further complications of caries, lateral periodontitis and various other lesions.

DENS IN DENTE

It is also known as dens invaginatus. The term dens in dente is used for the large invagination of dental tissue within a tooth



FIGURE 1.34: Coronal dens invaginatus seen on left maxillary lateral incisor

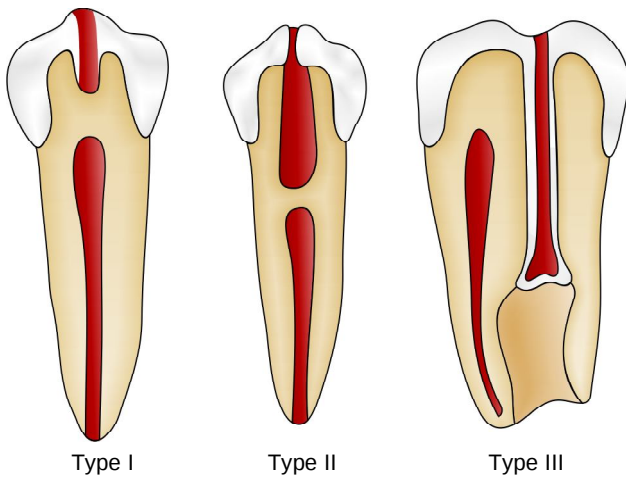


FIGURE 1.35: Various forms of dens invaginatus

giving a resemblance of a tooth within the tooth. It is an invagination of crown or root, which is lined by enamel. Ohlers described this condition for the first time in 1957.⁴⁹

Types

It is of two types:

1. Coronal: Invagination of crown portion (Fig. 1.34)
2. Radicular: Invagination of root portion.

Etiopathogenesis

It is hypothesized that before eruption, the lumen of invagination is filled with soft tissue similar to the dental follicle. This soft tissue later on loses its vascular supply and becomes necrotic.

Clinical Features

- Coronal dens invaginatus is most commonly seen with a prevalence of 0.04 to 10 percent.

- Occurrence is most common in maxillary dentition in decreasing order of lateral incisors, central incisors, premolars, canines and molars.
- It may be seen as an enlargement of the cingulum pit to a deep infolding extending towards the apex.
- Coronal dens invaginatus is divided into three types (Fig. 1.35):
 - Type I, where the invagination is seen in the crown.
 - Type II, where the invagination extends below cemento-enamel junction that may or may not communicate with the dental pulp.
 - Type III, where the invagination extends through the root and perforates in the apical or lateral radicular area without any communication with the pulp.
- Sometimes, the invagination may be so dilated that it does not permit the eruption of the tooth, in such cases it is termed as **dilated odontome**.
- Radicular dens invaginatus though rare, may be seen to arise secondary to proliferation of the Hertwig's epithelial root sheath. Altered enamel forms an invagination into the dental papilla.

Radiographic Features

- In coronal dens invaginatus, the radiograph shows the invagination into the crown involving enamel, dentin, with or without involvement of pulp with extension only into crown or up to the radicular area (Fig. 1.36).
- In radicular dens invaginatus, the radiograph shows enlarged roots.



FIGURE 1.36: Radiographic picture of coronal dens invaginatus affecting the maxillary lateral incisor



FIGURE 1.37: Mandibular premolar showing dens evaginatus

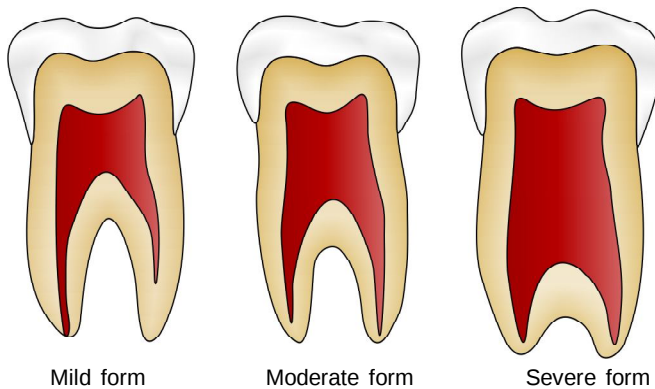


FIGURE 1.38: Various forms of taurodontism

Management

1. Small Type I invaginations should be sealed upon eruption to prevent caries and pulpal inflammation.
2. In case of large invaginations with caries, the carious lesion should be removed, calcium hydroxide base placed and the lesion restored.
3. When the invagination involves the pulp, endodontic treatment is recommended.
4. In case where the teeth have an open apex, apexification with calcium hydroxide is successful.
5. Larger invaginations require extraction of the tooth, if endodontic therapy is unsuccessful.

DENS EVAGINATUS (FIG. 1.37)

Dens evaginatus is the exact opposite of dens in dente. It is an elevation of enamel in the central groove or lingual ridge of the buccal cusp of premolar or permanent molar teeth.

Clinical Features

- It is usually bilateral and shows mandibular predominance.
- The elevation in the form of cusp consists of normal enamel, dentin and pulp.

- This anomaly is often associated with shovel shaped incisors in which the incisors show prominent lateral margins with hollowing in the center on lingual surface resembling scoop of shovel.

Management

1. Dens evaginatus may result in fracture of the tooth causing exposure of the pulp. In such cases, root canal therapy or apexification with calcium hydroxide is often recommended.
2. Grinding the tooth followed by direct or indirect pulp capping with calcium hydroxide cement has been suggested.
3. Placement of composite restoration to reinforce the tooth before it reaches occlusal level is also recommended.

TAURODONTISM

(*Tauro*= bull, *dont*= tooth). Taurodontism implies an anomaly where there is an enlargement of the body of the pulp chamber with apical displacement of the pulpal floor. It mostly occurs in multi-rooted teeth. It is also called 'bull tooth' as it resembles the molar of cud chewing animals.

Classification (Fig. 1.38)

It is divided into three types depending upon the degree of apical displacement of the pulpal floor as:

1. Mild (hypotaurodontism).
2. Moderate (mesotaurodontism).
3. Severe (hypertaurodontism).

Clinical Features

- Tooth generally appears rectangular in shape with the pulp chambers showing increased apico-occlusal height with bifurcation close to the apex of the root.
- The anomaly usually affects permanent teeth and rarely deciduous teeth.
- It may be unilateral or bilateral.
- It may occur isolated or may be associated with some syndromes.
- It has also been reported in association with cleft lip and palate.

Syndromes Associated with Taurodontism

- Amelogenesis imperfecta, hypoplastic type, type IE
- Amelogenesis imperfecta taurodontism, type IV
- Ectodermal dysplasia
- Klinefelter syndrome
- Oral-facial-digital syndrome, type II
- Down syndrome

Management

1. No specific treatment required.
2. During endodontic therapy, it is difficult to locate, instrument and obturate the pulp canals.
3. Removal of pulp tissue from the chamber also requires meticulous removal.

SUPERNUMERARY ROOTS

It refers to the development of an increased number of roots on a tooth compared with that classically described in dental anatomy.

Clinical Features

- Seen in both primary and permanent dentitions.
- Most commonly seen in third molars due to a developmental malformation. Other teeth affected are molars, mandibular cuspids and premolars.
- At times, the additional root is small and superimposed over other roots, hence difficult to diagnose.

Management

1. No specific treatment required.
2. Diagnosis is critical, as during endodontic procedures, failure to discover these additional canals often results in a lack of resolution of the associated inflammatory process.
3. During extractions, it is important to remove all the roots associated with the tooth, hence diagnosis of a supernumerary root becomes critical as it is not always evident radiographically.

DEVELOPMENTAL DEFECTS IN NUMBER OF TEETH

- Anodontia
- Supernumerary teeth
- Predeciduous dentition

ANODONTIA

It is also called as agomphosis, agomphiasis. In dentistry, anodontia, also called anodontia vera, is a rare genetic disorder characterized by the congenital absence of all primary or permanent teeth. Complete anodontia is usually part of a syndrome, usually hereditary hypohydrotic ectodermal dysplasia and seldom occurs as an isolated entity.

Partial anodontia, known as hypodontia or oligodontia, is the congenital absence of one or more teeth, which is relatively common. Congenital absence of all wisdom teeth, or third molars, is relatively common. **Hypodontia** is genetic in origin and usually involves the absence of 1 to 6 teeth (Fig. 1.39).



FIGURE 1.39: Hypodontia showing absence of teeth

Oligodontia is genetic as well and is the term most commonly used to describe conditions in which more than six teeth are missing.

Etiology

- Absence of the entire dental lamina which results in absence of an entire dentition.
- Absence of one or more tooth follicles resulting in partial anodontia.
- Absence of tooth follicles of the third molars, mandibular second premolars and maxillary lateral incisors as evolution occurs.

Syndromes Associated with Anodontia

- Cherubism
- Mulibrey nanism syndrome
- Gorlin-Chaudhry-Moss syndrome
- Acro-dermato-ungual-lacrimar tooth syndrome
- Ectodermal dysplasia (Margarita Island)
- Rieger syndrome
- Rothmund-Thomson syndrome
- Hay-Wells syndrome
- Schopf-Schulz-Passarge syndrome
- Rosselli-Gulienetti syndrome
- Rapp-Hodgkin ectodermal dysplasia syndrome
- Witkop's syndrome
- Ellis-van Creveld syndrome
- Sener syndrome
- Incontinentia pigmenti
- Focal dermal hypoplasia

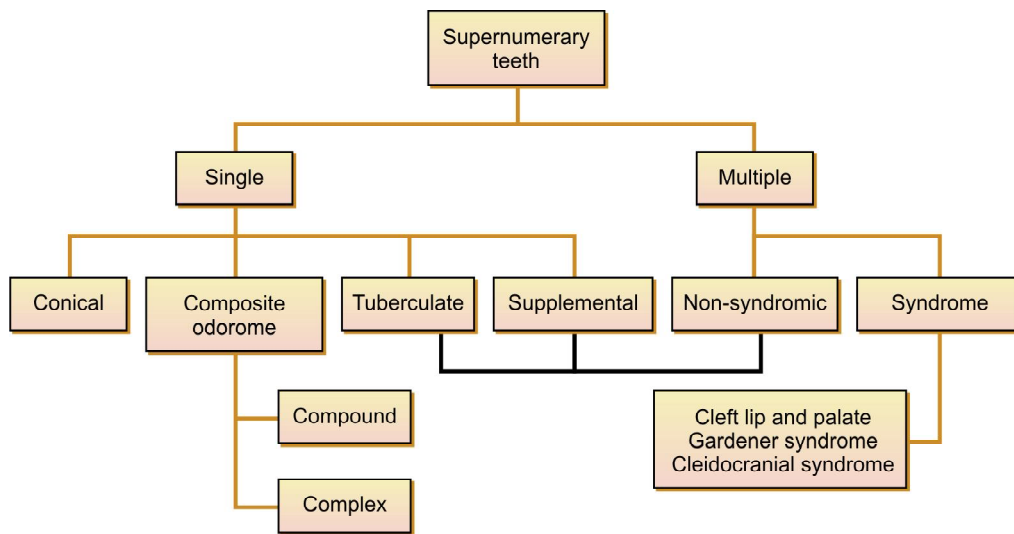


FIGURE 1.40: Schematic representation of classification of supernumerary teeth

- van der Woude syndrome
- Ehlers-Danlos syndrome, classic type
- Focal dermal hypoplasia
- Hutchinson Gilford syndrome.

Clinical Features

- One or more teeth missing in the dental arch, with no previous history of extraction or exfoliation.
- Hypodontia has a prevalence of 3.5 to 8 percent (excluding third molars) in the permanent dentition and less than 1 percent in the deciduous dentition (usually involving the mandibular incisors).
- 20 to 23 percent of the population shows missing third molars.
- Female predominance of 1.5:1 is seen.
- After the molars, second premolars and lateral incisors are most frequently absent.
- Hypodontia is also associated with microdontia, reduced alveolar development, increased freeway space and retained primary teeth.

Management

1. Management depends on the severity of the case.
2. Endodontic therapy followed by obturation with gutta-percha may be done in order to retain a deciduous tooth whose succedaneous tooth is missing. A full coverage crown may be placed to simulate the size of its succedaneous tooth.
3. Prosthetic treatment of the missing teeth may be required, which may include resin-bonded bridges or osseointegrated implants with associated prosthetic crowns.
4. In children, usually an implant is not recommended until full dental maturation.

SUPERNUMERARY TEETH

Definition

A supernumerary tooth is one that is additional to the normal series and can be found in almost any region of the dental arch.

Classification

See Fig. 1.40.

Etiology

- The etiology of supernumerary teeth is not completely understood.
- Various theories exist for the different types of supernumerary teeth. One theory suggests that the supernumerary tooth is created as a result of a dichotomy of the tooth bud.⁵⁰ Another theory is the hyperactivity theory, which suggests that supernumeraries are formed as a result of local, independent, conditioned hyperactivity of the dental lamina.^{51,52}
- Heredity may also play a role in the occurrence of this anomaly, as supernumeraries are more common in the relatives of affected children than in the general population. However, the anomaly does not follow a simple Mendelian pattern.

Clinical Features

- **Brook, 1974**, found that supernumerary teeth were present in 0.8 percent of primary dentitions and in 2.1 percent of permanent dentitions.⁵³
- Occurrence may be single or multiple, unilateral or bilateral, erupted or impacted and in one or both jaws.

- While there is no significant sex distribution in primary supernumerary teeth, males are affected approximately twice as frequently as females in the permanent dentition.
- In the primary dentition, morphology is usually normal or conical. There is a greater variety of forms presenting in the permanent dentition. However, it is comparatively uncommon in the deciduous dentition.
- Usually may be asymptomatic and may be discovered on routine radiographic examination.
- Multiple supernumerary teeth are rare in individuals with no other associated diseases or syndromes.
- The conditions commonly associated with an increased prevalence of supernumerary teeth include:
 - *Cleft lip and palate*: Supernumerary teeth associated with cleft lip and palate result from fragmentation of the dental lamina during cleft formation. The frequency of supernumerary permanent teeth in the cleft area in children with unilateral cleft lip or palate or both was found to be 22.2 percent.⁵⁴
 - *Cleidocranial dysplasia*: The frequency of supernumeraries in patients with cleidocranial dysplasia ranged from 22 percent in the maxillary incisor region to 5 percent in the molar region.⁵⁵
 - Gardner syndrome
- Supernumerary teeth in permanent dentition may be of the following types:
 - *Conical*: This small peg-shaped conical tooth is the most commonly found supernumerary tooth in the permanent dentition (Fig. 1.41). It develops with root formation ahead of or at an equivalent stage to that of permanent incisors and usually presents as a mesiodens. It may occasionally be found high and inverted into the palate or in a horizontal position. In most cases, however, the long axis of the tooth is normally inclined. The conical supernumerary can result in rotation or displacement of the permanent incisor, but rarely delays eruption.
 - *Tuberculate*: The tuberculate type of supernumerary possesses more than one cusp or tubercle. It is frequently described as barrel-shaped and may be invaginated. Root formation is delayed compared to that of the permanent incisors. Tuberculate supernumeraries are often paired and are commonly located on the palatal aspect of the central incisors. They rarely erupt and are frequently associated with delayed eruption of the incisors.
 - *Supplemental*: The supplemental supernumerary refers to a duplication of teeth in the normal series and is found at the end of a tooth series. The most common supplemental tooth is the permanent maxillary lateral incisor, but supplemental premolars and molars also occur. The majority of supernumeraries found in the



FIGURE 1.41: Peg lateral with over-retained deciduous lateral incisor

primary dentition is of the supplemental type and seldom remain impacted.

- *Odontoma*: Howard lists odontoma as the fourth category of supernumerary teeth. However, this category is not universally accepted. The term “odontoma” refers to any tumor of odontogenic origin. Most authorities, however, accept the view that the odontoma represents a hamartomatous malformation rather than a neoplasm. The lesion is composed of more than one type of tissue and consequently has been called a composite odontoma. Two separate types have been described: the diffuse mass of dental tissue which is totally disorganized is known as a complex composite odontoma (Fig. 1.42), whereas the malformation which bears some superficial anatomical similarity to a normal tooth is referred to as a compound composite odontoma.
- Another rare type of supernumerary teeth is a “third set of teeth” that forms underneath and pushes out the second set of teeth, much like the second set formed underneath which pushes out the first set of teeth.

Clinical Significance of Supernumerary Teeth

- **Failure of eruption**: The presence of a supernumerary tooth is the most common cause of failure of eruption of a maxillary central incisor. It may also cause retention of the primary incisor. The problem is usually noticed with the eruption of the maxillary lateral incisors together with failure of eruption of one or both central incisors. Supernumerary teeth in other locations may also cause failure of eruption of adjacent teeth.



FIGURE 1.42: Odontome in addition to the normal complement of teeth

- **Displacement:** The presence of a supernumerary tooth may cause displacement of a permanent tooth. The degree of displacement may vary from a mild rotation to complete displacement. Displacement of the crowns of the incisor teeth is a common feature in the majority of cases associated with delayed eruption.
- **Crowding:** Erupted supplemental teeth most often cause crowding. A supplemental lateral incisor may cause crowding in the upper anterior region. The problem may be resolved by extracting the most displaced or deformed tooth.
- **Dentigerous cyst formation** may be associated with supernumerary teeth. Primosch, 1981, reported an enlarged follicular sac in 30 percent of cases, but histological evidence of cyst formation was found in only 4 to 9 percent of cases.⁵⁵ Resorption of roots adjacent to a supernumerary may occur but it is extremely rare.

Radiographic Features

- The buccolingual position of unerupted supernumeraries can be determined using the parallax radiographic principle. The horizontal tube shift method utilizes two periapical radiographs taken with different horizontal tube positions, whereas an occlusal film together with a panorex view is routinely used for vertical parallax. If the supernumerary moves in the same direction as the tube shift it lies in a palatal position, but if it moves in the opposite direction then it lies buccally.
- Intraoral views may give a misleading impression of the depth of the tooth. A true lateral radiograph of the incisor region assists in locating the supernumeraries that are lying deeply in the palate and enables the practitioner to decide whether a buccal rather than a palatal approach should be used to remove them.

Management

1. Usually may be asymptomatic and may not require any treatment.
2. Supernumerary teeth may compromise secondary alveolar bone grafting in patients with cleft lip and palate. Erupted supernumeraries are usually removed and the socket site allowed healing prior to bone grafting.
3. The presence of an unerupted supernumerary in a potential implant site may compromise implant placement. The supernumerary may require removal prior to implant placement.
4. Extraction of the supernumerary tooth is recommended when:
 - Central incisor eruption has been delayed or inhibited
 - Altered eruption or displacement of central incisors is evident
 - There is associated pathology
 - Active orthodontic alignment of an incisor in close proximity to the supernumerary is envisaged
 - Its presence would compromise secondary alveolar bone grafting in cleft lip and palate patients
 - The tooth is present in bone designated for implant placement
 - Spontaneous eruption of the supernumerary has occurred.
5. Di Biase, 1971, found that 75 percent of incisors erupted spontaneously after removal of the supernumerary.⁵⁶ Eruption occurred on average within 18 months, provided that the incisor was not too far displaced and that sufficient space was available.
6. If there is adequate space in the arch for the unerupted incisor following supernumerary removal, space maintenance can be ensured by fitting a simple removable appliance. If the space is inadequate, the adjacent teeth will need to be moved distally to create space for incisor eruption. In that case, the primary canines may need to be extracted at the same time as the supernumerary tooth.
7. When there is adequate space and the incisor tooth fails to erupt, surgical exposure of the incisor and orthodontic traction is usually required.

PREDECIDUOUS DENTITION

Predeciduous teeth have been described as hornified epithelial structures without roots, occurring on the gingiva over the crest of the ridge, which may be easily removed. They are thought to arise from an accessory bud of the dental lamina ahead of the deciduous bud or from the bud of an accessory dental lamina.

Spouge and Feasby, 1966, believe that predeciduous teeth as an entity is a misinterpretation and such structures present

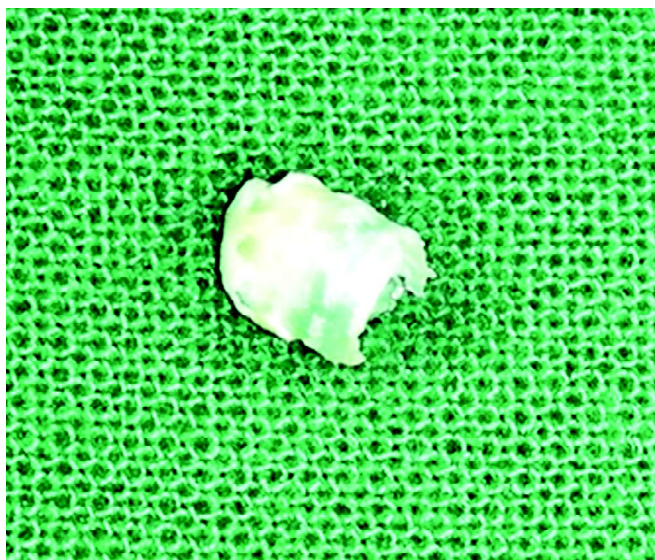


FIGURE 1.43: Extracted natal tooth

at birth undoubtedly represent only the dental lamina cyst of the newborn. This cyst commonly projects above the crest of the ridge, is white in color and is packed with keratin, so that it appears “hornified” and can be easily removed.⁵⁷

Natal teeth were first described by Massler, 1950.⁵⁸ They are also called as accessory teeth which may be present at or shortly after birth (Fig. 1.43).

For the purpose of nomenclature, natal teeth are considered as those teeth present in newborns and neonatal teeth are those which appear in the oral cavity within the first 30 days of life.

However, Neville states that this is an artificial distinction and all teeth should be called as natal teeth.

Spouge and Feasby, 1966, stated that natal teeth rarely represent predeciduous supernumerary teeth; rather most are prematurely erupted deciduous teeth and not supernumerary teeth.

Etiology

Several sources suggest a possible hereditary component. The Tlinget Indians in Alaska show a prevalence of 9 percent of their newborns having natal or neonatal teeth, 62 percent of them had affected relatives.⁵⁹

Environmental factors, especially polychlorinated biphenyls (PCBs) seem to increase the incidence of natal teeth. These children usually show other associated symptoms, such as dystrophic finger nails, hyperpigmentation, etc.

Natal teeth are sometimes associated with various syndromes like Jadassohn-Lewandowsky syndrome, Ellis-van Creveld syndrome, Hallermann-Streiff syndrome, etc.

Clinical Features

- Prevalence of natal teeth is around 1:700 to 1:30,000 depending on the type of study; the highest prevalence



FIGURE 1.44: Natal tooth with Riga Fede disease

being found in the study that relied on personal examination of patients.

- Kates et al, 1984, stated that 85 percent of the natal teeth are usually mandibular incisors, 11 percent are maxillary incisors and 4 percent are posterior teeth. The vast majority (90-99%) is primary teeth; only 1 to 10 percent are reported to be supernumerary teeth.⁶⁰
- *Riga Fede disease*: Sublingual ulceration may occur in infants as a result of chronic mucosal trauma from adjacent anterior primary teeth, often associated with nursing. These distinctive ulcerations of infancy have been termed Riga Fede disease and should be considered a variation of the traumatic eosinophilic ulceration (Fig. 1.44).

Histopathologic Features

Histologically the enamel in natal and neonatal teeth is normal for the age of the child, but when the teeth erupt prematurely the uncalcified enamel matrix wears off because mineralization is not complete. The teeth turn yellow-brown and the enamel continuously breaks down. The usually increased mobility causes histologic changes in the cervical dentin and cementum. Hertwig's sheath may degenerate and root formation may be prevented.

Management

1. Natal teeth must be approached individually with sound clinical judgment guiding appropriate therapy.
2. According to Massler and Savara, if they represent the deciduous dentition, they should not be extracted hastily, if they do not pose a problem to the mother or the infant.

3. If the teeth are mobile, there is a high risk of aspiration and extraction of the teeth is recommended.
4. If the teeth are stable, they should be retained.
5. Riga Fede disease can be resolved with appropriate measures. If teeth are conical, they can be ground off to prevent trauma. Some authors recommend splinting or disking of the affected teeth to prevent traumatic injuries. If trauma does not resolve, extraction of the teeth is recommended.
6. Extraction of natal teeth should usually be followed by administration of vit. K injections because, in newborns, liver enzymes are functionally not well developed and hence deficiency of vit. K derived factors like Factors VII, IX and X are likely. However, hypothermia should no longer be a concern, since newborns are routinely given vitamin K to prevent this problem.
7. Teeth that are stable beyond 4 months have a good prognosis. Esthetically they are not pleasing due to their discoloration.

DEVELOPMENTAL DEFECTS IN STRUCTURE OF TEETH

- Amelogenesis imperfecta
- Environmental enamel hypoplasia
- Dentinogenesis imperfecta
- Dentin dysplasia
- Regional odontodysplasia
- Dentin hypocalcification

AMELOGENESIS IMPERFECTA

Amelogenesis imperfecta (AI) is a diverse collection of inherited diseases that exhibit quantitative or qualitative tooth enamel defects in the absence of systemic manifestations. Also known by varied names such as hereditary enamel dysplasia, hereditary brown enamel, hereditary brown opalescent teeth, this defect is entirely ectodermal, since mesodermal components of the teeth are basically normal. The AI trait can be transmitted by either autosomal dominant, autosomal recessive or X-linked modes of inheritance. Genes implicated in autosomal forms are genes encoding enamel matrix proteins: enamelin and ameloblastin, tuftelin, MMP-20 and kallikrein-4.

Tooth enamel is the most highly mineralized structure in the human body, with 85 percent of its volume occupied by unusually large, highly organized hydroxyapatite crystals.^{61,62} The physical properties and physiological function of enamel are directly related to the composition, orientation, disposition, and morphology of the mineral components within the tissue.⁶³ During organogenesis, the enamel transitions from a soft and pliable tissue to its final form, almost entirely devoid of protein. The final composition of enamel is a reflection of the unique

TABLE 1.4: Classification of amelogenesis imperfecta (Witkop and Sauk)

Type I Hypoplastic

- IA Hypoplastic, pitted autosomal dominant
- IB Hypoplastic, local autosomal dominant
- IC Hypoplastic, local autosomal recessive
- ID Hypoplastic, smooth autosomal dominant
- IE Hypoplastic, smooth X-linked dominant
- IF Hypoplastic, rough autosomal dominant
- IG Enamel agenesis, autosomal recessive

Type II Hypomaturation

- IIA Hypomaturation, pigmented autosomal recessive
- IIB Hypomaturation
- IIC Snow capped teeth, X-linked
- IID Autosomal dominant?

Type III Hypocalcification

- IIA Autosomal dominant
- IIB Autosomal recessive

Type IV Hypomaturation—Hypoplastic with taurodontism

- IVA Hypomaturation—Hypoplastic with taurodontism, autosomal dominant
- IVB Hypoplastic—Hypomaturation with taurodontism, autosomal dominant

molecular and cellular activities that take place during its genesis. These activities are controlled by a regulated expression of multiple genes.⁶⁴ Deviation from this pattern leads to amelogenesis imperfecta. Witkop and Sauk listed the varieties of AI, divided according to whether the abnormality lay in a reduced amount of enamel (hypoplasia), deficient calcification (hypocalcification), or imperfect maturation of the enamel (hypomaturation) and also recognized combined defects (Table 1.4).⁶⁵

Aldred et al, 2003 has given a classification based on:⁶⁶

- Mode of inheritance
- Phenotype—Clinical and Radiographic
- Molecular defect (when known)
- Biochemical result (when known)

Amelogenesis imperfecta (AI) is a developmental, often inherited disorder affecting dental enamel. It usually occurs in the absence of systemic features and comprises diverse phenotypic entities.

Etiopathogenesis

- The trait of AI can be transmitted by an autosomal-dominant, autosomal-recessive, or X-linked mode of inheritance.
- Some of the genes encoding specific enamel proteins have been indicated as candidate genes for amelogenesis imperfecta. Mutational analyses within studied families have supported this hypothesis.

- The amelogenin gene is a tooth-specific gene expressed in pre-ameloblasts, ameloblasts and in the epithelial root sheath remnants;⁶⁷ while a low expression of amelogenin mRNAs has been recently shown in odontoblasts.^{68,69} To date, there are 14 AMELX-associated AI mutations.^{70,71}
- The enamelin (ENAM) gene is a tooth-specific gene expressed predominantly by the enamel organ and at a low level, in odontoblasts. The human ENAM gene is localized on chromosome 4 (4q13.3). One autosomal-inherited form of AI, namely, autosomal-dominant amelogenesis imperfecta (ADAI), was linked to a 4Mb region on 4q21. The ENAM gene has been mapped within this locus by radiation hybrid analysis (RHA) and fluorescent *in situ* hybridization (FISH) and was therefore considered a candidate gene for this type of AI.^{72,73}
- The ameloblastin (AMBN) gene is expressed at high levels by ameloblasts and at low levels by odontoblasts and pre-odontoblasts, while moderate expression is also observed in Hertwig's epithelial root sheath, and in odontogenic tumors, such as in ameloblastomas.⁷⁴ The human AMBN is localized on chromosome 4 at locus 4q21 near other genes associated with mineralized tissues: osteopontin, bone sialoprotein and bone morphogenetic protein 3. AMBN maps within the critical region for autosomal-dominant AI and therefore is considered as a candidate gene. However, it was excluded from a causative role by mutational analyses within the families studied by Mårdh-Kärman C et al.⁷⁵
- The KLK4 gene is located near the telomere of chromosome 19 (19q13.3–19q13.4) downstream of the KLK2 gene and is considered a member of the human tissue kallikrein gene family.^{76,77} KLK4 is expressed by both ameloblasts and odontoblasts.
- Due to abnormal enzymic activity, the crystallites of the enamel grew to the normal length but incompletely in thickness.
- MMP-20 gene codes for a calcium-dependent proteinase that is a member of the matrix metalloproteinases family (MMPs). Additionally, no other intact, physiologically normal, tissue has been demonstrated to express MMP-20, apart from ameloblasts, pre-ameloblasts and odontoblasts, whereas the expression of MMP-20 in human odontogenic tumors and carcinoma cell lines originating from the tongue has recently been described.^{78,79}
- The DLX3 gene is a member of the family of homeobox genes that are homologous to the distalless (Dll) gene of *Drosophila*, known to be expressed during development of the chondrocranium, dermatocranium, sensory organs, brain, limbs and appendages and in the processes of osteogenesis and hematopoiesis.⁸⁰ Mutation within the human DLX3 gene homeodomain is associated with

amelogenesis imperfecta (hypoplastic-hypomaturational type), with taurodontism (AIHHT).

- However, AMELX, AMBN, ENAM, KLK4 and MMP-20 were excluded from a causative role in two families with autosomal-dominant hypocalcified AI, suggesting that this type of AI is caused by mutation of a gene that is either not known or not considered to be a major contributor to enamel formation.⁸¹
- Mutations in the amelogenin gene (AMELX) cause X-linked amelogenesis imperfecta, while mutations in the enamelin gene (ENAM) cause autosomal-inherited forms of amelogenesis imperfecta. Recent reports involve kallikrein-4 (KLK4), MMP-20 and DLX3 genes in the etiologies of some cases.⁸²

Clinical Features

- The predominant clinical manifestations of affected individuals are enamel hypoplasia (enamel is seemingly correctly mineralized but thin), hypomineralization (subdivided into hypomaturational and hypocalcification), or a combined phenotype, which is seen in most cases.
- The prevalence of this condition has been estimated to range from 1 in 78 to 1 in 14,000, depending on the population studied. Hypoplastic (AI) represents 60 to 73 percent of all cases, hypomaturational (AI) represents 20 to 40 percent and hypocalcification (AI) represents 7 percent.⁸³
- The distribution of AI types is known to vary among different populations. In a study in Sweden, 63 percent of the cases were inherited as autosomal-dominant. In contrast, in a study in the Middle East, the most common prevalent type of AI was found to be autosomal-recessive.

Radiographic Features

- The enamel may appear totally absent on the roentgenogram, or when present, may appear as a very thin layer, chiefly over the tips of the cusps and on the interproximal surfaces.
- In other cases the calcification of enamel may be so affected that it appears to have the same approximate radiodensity as the dentin, making differentiation between the two difficult.

The four major clinical variants have typical clinical and radiographic features.

1. **Hypoplasia:** Enamel thickness is reduced such that the dentin shows through and imparts a yellowish-brown color to the tooth. The enamel may be pitted, rough, smooth or glossy. Radiographs demonstrate a square shaped crown, a thin layer of enamel of normal density and low or absent cusps (Figs 1.45 and 1.46).



FIGURE 1.45: Clinical appearance of teeth affected by amelogenesis imperfecta

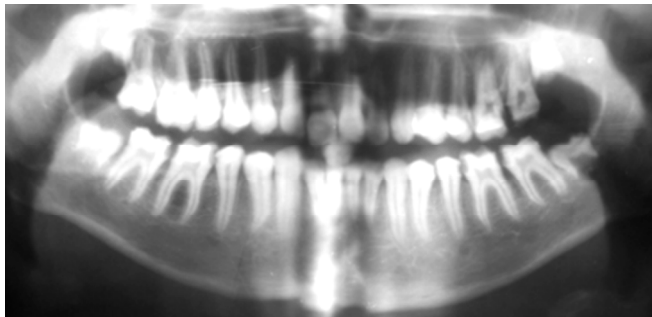


FIGURE 1.46: Radiographic appearance of teeth affected by amelogenesis imperfecta

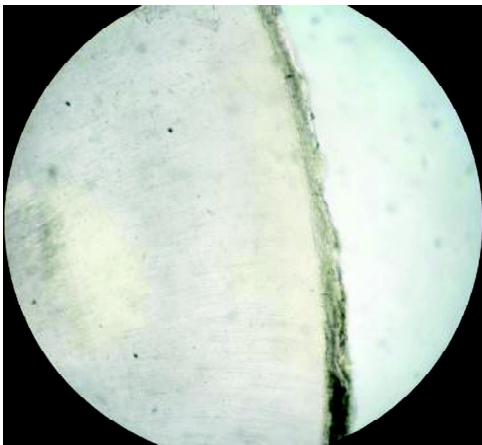


FIGURE 1.47: Ground section of amelogenesis imperfecta showing a reduced enamel thickness and composed of laminations of irregularly arranged enamel prisms

2. *Hypomaturation:* The enamel is softer with a normal thickness but mottled appearance. The teeth may appear to be snow-capped. Radiographs reveal enamel whose density is the same as that of dentin.

3. *Hypocalcification:* Enamel tends to fracture away shortly after it comes into function. An explorer point under pressure can penetrate the soft enamel. Yet, caries is unusual. Radiographically, enamel thickness appears to be normal but the density is even less as compared to dentin.
4. *Hypomaturation/hypocalcification:* The term is referred to depending on the dominant defect. The enamel is usually mottled and discolored. Both the deciduous and permanent dentitions are involved diffusely. In the hypomaturation hypoplastic pattern, the predominant defect is one of enamel hypomaturation in which the enamel appears as mottled yellowish-white to yellow-brown. Pits are seen frequently on the buccal surfaces of the teeth. Radiographically, the enamel appears similar to dentin in density, and large pulp chambers may be seen in single rooted teeth in addition to varying degrees of taurodontism. In the hypoplastic-hypomaturation pattern, the predominant defect is one of enamel hypoplasia in which the enamel is thin; the enamel that is present demonstrates hypomaturation. Except for the decrease in the thickness of enamel, this pattern is similar to the hypomaturation-hypoplastic variant.⁸⁴

Histopathologic Features

- Histologically, a ground section of teeth involved shows very thin enamel composed of laminations of irregularly arranged enamel prisms (Fig. 1.47).⁸⁵
- SEM studies of the extracted deciduous teeth in a case of autosomal recessive rough hypoplastic amelogenesis imperfecta showed the exposed outer enamel surface with irregularly shaped globular protrusions. At the cervical region of the crown, a series of wavy, parallel ridges was seen in the enamel regions. The cementum area was clearly distinguishable from the more coronal region by its mottled and fibrillar pattern and the tendency for the cementum to overlap the ridged coronal structure along the cervical line. Enamel had a high organic content with some abnormal prism formation. The dentinoenamel junction was sharply defined and easily identifiable because of the more homogenous appearance of the enamel matrix, as compared with that of the dentin with its array of collagen fibrils.⁸⁶
- The histology of autosomal dominant hypomaturation—hypoplasia type of AI with taurodontism, definitively described by Winter et al, comprises areas of severe hypomineralization with a pore volume of between 1 percent and 25 percent. They described a normal prismatic structure to the enamel, but with considerable post-calcification organic content and occasional bands of globular defects. The dentine was also reported as being defective, with a decreased number of tubules, an increased amount of

intertubular dentin, dilatations and cellular inclusions. All these findings were more marked in the radicular dentin. The pulp was normal but enlarged in size.⁸⁷

Management

1. Management usually involves complete oral rehabilitation by way of full coverage crowns, direct and indirect veneers and bonded esthetic restorations, depending on the condition of the individual tooth and the age of the patient.
2. Types ID, IE, IG, IIA, IIIB and IVB demonstrate very thin enamel or highly defective enamel, which leads to rapid attrition. These variants require full coverage as soon as is practical. If the treatment is delayed, a loss of usable crown length occurs. In those patients without sufficient crown lengths, full dentures (overdentures in some cases), often become the only satisfactory approach.
3. The other types of AI demonstrate less rapid tooth loss and the esthetic appearance is the prime consideration. In some cases, a lack of good enamel bonding of veneers occurs and does not result in a durable restoration. The use of glass ionomer cements with dentinal adhesives often overcomes this weakness.
4. Thus, the dentist has to balance the decision for early intervention and the long-term survival of the restorations. Dental practitioners should consider the social implications for these patients and intervene to relieve their suffering.

ENVIRONMENTAL ENAMEL HYPOPLASIA

This term implies the defective formation of organic enamel matrix of teeth. It is of two basic types:

1. Environmental, i.e. influenced by environmental forces.
2. Hereditary

Ameloblasts in the developing tooth germ are extremely sensitive to external stimuli and many factors can result in abnormalities in enamel.

Etiology

The etiological causes may be considered as:

Systemic

- Birth related trauma: Breech presentations, hypoxia, multiple births, premature birth, prolonged labor
- Chemicals: Antineoplastic chemotherapy, fluoride, lead, tetracycline, thalidomide, vitamin D
- Chromosomal abnormalities: Trisomy 21
- Infections: Chickenpox, cytomegalovirus (CMV), gastrointestinal infections, measles, pneumonia, respiratory infections, rubella, syphilis, tetanus

- Inherited diseases: Amelo-cerebro-hypohydrotic syndrome, epidermolysis bullosa, mucopolysaccharidosis IV, phenylketonuria, pseudohypoparathyroidism, tuberous sclerosis, vitamin D dependent rickets
- Malnutrition: Generalized malnutrition, vitamin D deficiency, vitamin A deficiency
- Metabolic disorders: Cardiac disease, celiac disease, hepatobiliary disease, hypocalcemia, hypothyroidism, hypoparathyroidism, maternal diabetes, toxemia of pregnancy
- Neurologic disorders: Cerebral palsy, mental retardation, sensorineural hearing defects.

Local

- Local acute mechanical trauma: falls, neonatal mechanical ventilation, surgery
- Electric burn
- Irradiation
- Local infection: acute neonatal maxillitis, periapical inflammatory disease

The enamel develops in three major stages:

1. Matrix formation
2. Mineralization
3. Maturation

The timing of the ameloblastic damage has a great impact on the location and appearance of defect in the enamel. The cause of the damage is not particularly important as many local and systemic stimuli can result in defects having similar clinical appearances. The final enamel presents all significant insults received during tooth developments as various defects in it. *Deciduous enamel contains a neonatal ring and the rate of enamel apposition is estimated to be 0.023 mm per day. This helps the clinician to accurately time an insult to the deciduous teeth within a week.*

Clinical Features

- When examining enamel defects, it is imperative to clean the dentition thoroughly and dry it with gauze. A good source of light from a dental operatory is ideal. Plaque disclosing agents may be used for minor defects.
- Depending on the extent and stage at which enamel formation has been disrupted, all enamel defects can be clinically classified into one of three patterns:
 - *Hypoplasia*: Appears as pits, grooves or larger areas of missing enamel.
 - *Diffuse opacities*: Appear as variations in translucency of enamel. The thickness of enamel is normal, but with increased white opacity which has no clear demarcation from the adjacent normal enamel.
 - *Demarcated opacities*: Appear as areas of decreased translucence, increased opacity and a sharp boundary

with the adjacent enamel. The thickness of enamel is normal and the affected opacity may be white, cream, yellow or brown.

- Environmental enamel abnormalities are extremely common. Small and Murray, 1979, reported that between the ages of 12 to 15 years, the prevalence of enamel defects in the permanent dentition was 68.4 percent with 67.2 percent showing opacities, 14.6 percent showing hypoplasia and 13.4 percent showing both hypoplasia and opacities.⁸⁸
- Crowns of deciduous teeth start developing from 14th week of gestation till approximately when the child is 12 months of age. Crowns of permanent dentition start developing from 6 months to approximately 15 years of age. The site of coronal damage correlates with the area of ameloblastic activity at the time of injury.
- Systemic influences like exanthematous fevers that often occur during the first-two years of life commonly present as horizontal rows of pits or diminished enamel on the anterior teeth and first molars.
- A similar pattern of enamel defects appears on the cuspids, bicuspid and second molars when the event occurs at the age of 4 to 5 years.
- Another frequent appearance is the Turner's tooth caused due to Turner's hypoplasia of the affected tooth. Turner was the dental clinician who widely publicized the presence of such a pattern of hypoplasia. Turner's hypoplasia can be described as enamel defects seen in the permanent teeth due to disruption of permanent teeth caused by periapical inflammatory disease of the overlying deciduous tooth. Quite a variation of defects occurs as white, yellow or brown discoloration to extensive hypoplasia depending upon the time and severity of the insult. Usually seen in the permanent premolars because of their relationship to overlying deciduous molars.
- Turner's teeth may also occur due to traumatic injury to deciduous teeth commonly seen in permanent maxillary central incisors. As the permanent incisors develop lingual to the primary teeth, the facial surface of the maxillary incisors is the location frequently affected appearing as a zone of white or yellowish brown discoloration with or without an area of horizontal enamel hypoplasia. Trauma leading to displacement of the already formed hard tooth substance may result in dilaceration and severe trauma early in the development of tooth may result in such disorganization of the bud that the resultant product may result in complex odontoma.
- Hypoplasia may also arise secondary to the use of therapeutic radiation or chemotherapy provided against childhood cancer, most commonly in patients under the age of twelve, with extensive defects occurring in those under five years of age. Doses as low as 0.72 Gy are associated

with mild developmental defects in both enamel and dentin. Apart from dental defects, hypodontia, microdontia mandibular hypoplasia, reduction of the vertical development of the face and reduced alveolar bone growth may occur secondary to radiation.

- In 1901, Dr Frederick McKay, first reported Colorado brown stains which were later found by HV Churchill in 1930 to have been caused by high concentrations of fluoride (13.7 ppm).⁸⁹ Dr Trendley H Dean carried out a shoe leather survey in 1931 and recommended the presence of an optimum level of 1ppm F in drinking water to minimize caries, strengthen teeth at the same time avoiding the risk of dental fluorosis.⁹⁰ Dental fluorosis is the presence of significant enamel defects resulting from ingestion of excessive amounts of fluorides during stages of tooth formation. The appearance of these defects depends upon the level of fluoride in water as well as the time and duration for which the developing tooth was exposed to the excessive levels of fluorides. Dental fluorosis may occur due to excessive levels of fluoride in water, but apart from this a significant ingestion of fluoride may occur from fluoride toothpastes, fluoride supplements, infant formulae, soft drinks, fruit juices and industrial environmental emissions. These may create significant enamel defects through retention of amelogenin proteins in the enamel structure, leading to the formation of hypomineralized enamel. These alterations create a permanent hypomaturation of the enamel in which there is an increased surface and subsurface porosity of the enamel. This enamel structure alters the light reflection and creates the appearance of white, chalky areas. The teeth affected by fluorosis are caries resistant and the altered tooth structure appears as areas of lustreless white opaque enamel that may have zones of yellow to dark brown discoloration. True enamel hypoplasia is uncommon but can occur as deep irregular brownish pits. Clinical diagnosis is usually based on history of excessive fluoride intake.
- Congenital syphilis results in a distinct pattern of hypoplasia that is extremely rare currently. Anterior teeth are called as Hutchinson's incisors and exhibit crowns that are shaped like straight edged screw-drivers with the greatest circumference present in the middle one-third of the crown and a constricted incisal edge. The middle portion of the incisal edge often demonstrates a central hypoplastic notch. Altered posterior teeth are called as mulberry molars (Moon's molars, Fournier's molars) and demonstrate a constricted occlusal table with a disorganized surface anatomy that resembles the bumpy surface of a mulberry.
- Syndromes associated with hypoplasia:
 - Down syndrome
 - Tuberous sclerosis

- Epidermolysis bullosa
- Hurler syndrome
- Hunter syndrome
- Treacher Collins syndrome
- Phenylketonuria
- Pseudohypoparathyroidism
- Trichodonto-osseous syndrome
- Vitamin D dependent rickets
- Lesch-Nyhan syndrome
- Fanconi's syndrome
- Sturge-Weber syndrome
- Turner's syndrome

Management

1. Management usually involves restoration of the esthetic defect, depending on the condition of the individual tooth and the age of the patient.
2. Sometimes surface microabrasion is sufficient to eliminate a minor defect in the enamel.
3. Further cosmetic restoration may be done with the help of acid-etched composite resin restorations, veneers and full crowns.

DENTINOGENESIS IMPERFECTA (FIG. 1.48)

Dentinogenesis imperfecta is a hereditary developmental disturbance of dentin in the absence of any systemic disorder. This condition causes the teeth to be discolored (most often a blue-gray or yellow-brown color) and translucent. Teeth are also weaker than normal, making them prone to rapid wear, breakage and loss. These problems can affect both primary teeth and permanent teeth.

Classification

Shields, 1973, have described three types of dentinogenesis imperfecta:⁹¹

1. Type I occurs in people who have osteogenesis imperfecta, a genetic condition in which bones are brittle and easily broken.
2. Dentinogenesis imperfecta type II occurs in people without other inherited disorders and without any association genetically with osteogenesis imperfecta. A few families with type II have progressive hearing loss in addition to dental abnormalities.
3. Type III was first identified in a population in Brandywine, Maryland. Some researchers believe that dentinogenesis imperfecta type II and type III, along with a similar condition called dentin dysplasia type II, are actually forms of a single disorder.



FIGURE 1.48: Clinical picture of dentinogenesis imperfecta showing opalescent dentin

A revised classification mentions only dentinogenesis imperfecta 1 which corresponds to Shields type II and dentinogenesis imperfecta 2 which corresponds to Shields type III.

Another classification was given by Witkop in 1975 that divides dentin defects into three types:⁹²

1. Dentinogenesis imperfecta
2. Hereditary opalescent teeth
3. Brandywine isolate

Etiology

- Mutations in the DSPP gene (gene map locus 4q21.3) cause dentinogenesis imperfecta. They have been identified in people with type II and type III dentinogenesis imperfecta. Mutations in this gene are also responsible for dentin dysplasia type II. Dentinogenesis imperfecta type I occurs as part of osteogenesis imperfecta, which is caused by mutations in one of several other genes.
- The DSPP gene provides instructions for making proteins like dentin phosphoprotein, dentin sialoprotein and dentin sialophosphoprotein that are essential for normal tooth development. These proteins are involved in the formation of dentin. DSPP mutations alter the proteins made from the gene, leading to the production of abnormally soft dentin. It is unclear how DSPP mutations are related to hearing loss in some families with dentinogenesis imperfecta type II.
- This condition is inherited in an autosomal dominant pattern. In most cases, an affected person has one parent with the condition.
- Sauk et al, 1976, found an increase in glycosaminoglycans in EDTA soluble dentin in the teeth from patients of dentinogenesis imperfecta and less glycosaminoglycans in EDTA insoluble residue.⁹³

Clinical and Radiographic Features

- Dentinogenesis imperfecta affects an estimated 1 in 6,000 to 8,000 children.
- The teeth usually involved and more severely affected are deciduous teeth in type 1, whereas in type 2 both the dentitions are equally affected.
- Common clinical features are bluish-gray teeth, amber-colored teeth, bulbous teeth crowns, absent tooth roots, absent root canals, absent pulp chambers, too small tooth roots, too small root canals, too small pulp chambers, enamel separation from the dentin, malaligned teeth, recurring dental abscess, brittle bones and blue sclera.
- *Dentinogenesis imperfecta 1*: Blue-gray or amber brown and opalescent teeth with bulbous crowns. Radiograph reveals narrow roots, small pulp chambers and root canals which may be completely obliterated. Studies of dentin have revealed an increase in as much as 60 percent of water content above the normal level, whereas the inorganic content is less than that of normal dentin. Likewise, the density, X-ray absorption and hardness of dentin are low. Microhardness of dentin is similar to cementum which explains the rapid attrition of the affected teeth.
- *Dentinogenesis imperfecta 2*: The crowns of deciduous and permanent teeth wear rapidly after eruption and multiple pulp exposures may occur. The dentin is amber and smooth. Radiographs of deciduous dentition reveal very large pulp chambers and root canals. The permanent teeth have pulpal spaces that are small or completely obliterated. Non-mineralized pulp chambers and canals are seen giving a general appearance of *shell teeth* (Fig. 1.49).

Histopathologic Features

- *Dentinogenesis imperfecta 1*: Shows the appearance of normal enamel except for a change in shade which is a manifestation of the dentinal disturbance. Dentin shows irregular tubules with large areas of uncalcified matrix. The tubules are larger in diameter and less numerous than normal dentin. They may be completely absent in few areas. Cellular inclusions probably odontoblasts are also seen and the pulp chamber is usually almost obliterated by the contin



FIGURE 1.49: Radiographic picture of dentinogenesis imperfecta

ued deposition of the dentin. Odontoblast may degenerate readily and become entrapped in disorganized dentin matrix.

- *Dentinogenesis imperfecta 2*: Histopathology has not been adequately documented.

Management

1. Early and accurate diagnosis of dentinogenesis imperfecta is of utmost importance to enable proper preventative interventions and optimum dental handling.
2. Providing optimal oral health treatment for dentinogenesis imperfecta frequently includes preventing severe attrition associated with enamel loss and rapid wear of the poorly mineralized dentin, rehabilitating dentitions that have undergone severe wear, optimizing esthetics and preventing the common dental problems associated with caries and periodontal disease.
3. Placement of restorations may be compromised due to inadequate adhesion between dentin and the restorative material.
4. Prefabricated stainless steel crowns may be placed on deciduous molars to prevent attrition and collapse of the bite, as also to improve function.
5. Full coverage cast metal crowns are preferred on permanent posterior teeth; and porcelain fused to metal crowns may be used for the anterior teeth.
6. Endodontic treatment is occasionally necessary and has a guarded prognosis if initiated after pulp canal obliteration has occurred.

DENTIN DYSPLASIA

Dentin dysplasia (DD) is a genetic disorder of teeth, characterized by presence of normal enamel but atypical dentin with abnormal pulpal morphology. In 1920 Balchsmiede first reported 8 cases as “root less teeth”.⁹⁴ Later, Rushton, in 1939, described it as “Dentinal Dysplasia” (DD).⁹⁵

Classification

Carrol et al, published an extensive review of literature and proposed a subclassification based on the radiographic findings. They proposed 2 basic types: Type 1 was classified into 4 subtypes; 1a, 1b, 1c and 1d.⁹⁶

- In type 1a, there is a complete obliteration of the pulp and usually little or no root development.
- The Type 1b variant has a horizontal, crescent shaped, radiolucent line, which separates normal coronal dentin from abnormal radicular dentin. The roots are short, conical and rudimentary.
- Teeth affected by type 1c variant show 2 crescent-shaped horizontal radiolucent lines with their concavities toward

each other at the cemento-enamel junction and the roots one half the normal length.

- Type 1d is characterized by normal root formation, which sometimes may be bulbous in the coronal third. Within the pulp canal “a stone” may be found. In this type of DD, the pulp chamber is usually not obliterated and normal root formation occurs. This is the least severe form of DD. In these cases, the pulp around the stones is healthy. In other cases, the denticle is continuous with dentinal walls.
- The second type of DD, DD2 is characterized radiographically by extension of the pulp chamber into the root, pulp stones and sudden constriction of the chamber, which forms a thin radiolucent radicular structure.
- Dean et al⁹⁷ 1997, suggested that an updating of the nomenclature for the developmental disturbances of dentin is indicated, comparable to that presented by Aldred and Crawford, 1995, for developmental disturbances in amelogenesis imperfecta.

Etiology

- The similarity of the primary dentition phenotype between dentinogenesis imperfecta 1 (DGI1) and type II dentin dysplasia suggested that the gene for dentin dysplasia, type II is allelic with the gene for dentinogenesis imperfecta, Shields type II (DGI1), the isolated form of dentinogenesis imperfecta that has been shown by linkage studies to be encoded by a gene on 4q13–q21. Microsatellite markers specific for the area of 4q linked to DGI1 were used. Dean et al, concluded that any candidate gene for DGI1 should also be considered a candidate gene for dentin dysplasia, type II.
- On the basis of the phenotypic overlap between, and shared chromosomal location with dentinogenesis imperfecta type II, it has been proposed that dentin dysplasia type II and dentinogenesis imperfecta type II are allelic. The substitution in the hydrophobic signal peptide domain caused a failure of translocation of the encoded proteins into the endoplasmic reticulum. The authors hypothesized that this would most likely lead to a loss of function of both dentin sialoprotein and dentin phosphoprotein.
- Dentin dysplasia usually demonstrates an autosomal dominant inheritance.
- The abnormal root morphology is postulated secondary to the abnormal differentiation and/or function of the ectomesenchymally derived odontoblasts.

Clinical Features

- Dentin dysplasia type I (radicular type) is characterized by the presence of primary and permanent teeth with normal appearance of the crown but no or only rudimentary root development, incomplete or total obliteration of the pulp



FIGURE 1.50: Clinical features of dentin dysplasia

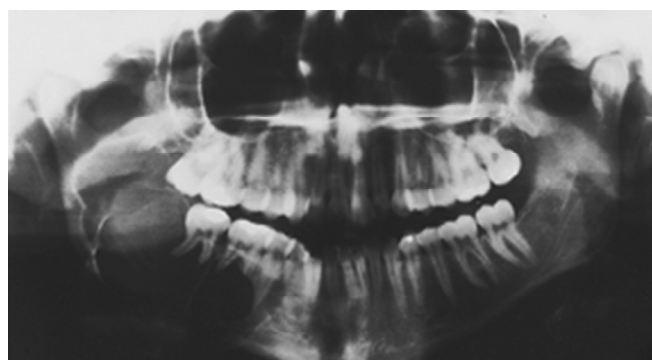


FIGURE 1.51: Radiographic picture of dentin dysplasia showing almost complete obliteration of the pulp chamber

chamber and periapical radiolucent areas or cysts. The pulp chamber is sometimes described as having a “crescent shaped” appearance.

- Dentin dysplasia type II (coronal type) is characterized by primary teeth with complete pulpal obliteration and brown or amber bluish coloration similar to that seen in hereditary opalescent dentin. The permanent teeth have a normal appearance or a slight amber-coloration, the roots are normal in size and shape with a “thistle-tube” shaped pulp chamber with pulp stones (Figs 1.50 and 1.51). In the deciduous dentition, coronal dentin dysplasia bears a resemblance to Dentinogenesis Imperfecta type II.
- Generally no signs of gingivitis or periodontitis are present. Mobility of teeth may be present due to short, malformed or apparently absent roots.

Radiographic Features

Type 1: Roots are short, blunt and conical. In deciduous teeth, pulp chambers and root canals are completely obliterated; in permanent teeth they may be crescent shaped.

Type 2: The pulp chamber of the deciduous teeth become obliterated in deciduous teeth, while in permanent teeth, large

pulp chamber is seen in coronal portion of the tooth—referred to as “thistle tube” appearance. Pulp stones may also be found.

Histopathologic Features

Type I: Normal dentinal tubule formation is blocked and new dentin forms around obstacles. This appearance is typically known as “lava flowing around boulders”.

Type II: In deciduous teeth, the pattern is similar to that in dentinogenesis imperfecta. In permanent teeth, enamel and coronal dentin are normal. Radicular dentin is atubular, amorphous and hypertrophic. Adjacent to the pulp, numerous areas of interglobular dentin are seen. Pulp stones develop in any portion of the chamber.

Management

1. The sequelae of dentin dysplasia are difficult to manage and provide a challenge for the dentist concerning not only restorative and endodontic treatment but also prosthetic treatment after loss of teeth.
2. Successful oral rehabilitation with complete dentures after extraction of all teeth and curettage of cysts has been described.
3. Cast partial dentures may be provided if the basal bone does not provide adequate support for acrylic partial dentures.
4. Although various treatment strategies including conventional endodontic therapy, periapical curettage or preventive regimen have been proposed to maintain the teeth for as long as possible, early exfoliation of the teeth and maxillomandibular atrophy as a consequence of abnormal root development, periapical abscesses or cystic formations are characteristics of dentin dysplasia type I.
5. When implant supported prostheses are planned in patients affected by dentin dysplasia type I bone regenerative therapy is required. Munoz-Guerra et al. reported successful treatment of a 24-year-old girl after onlay bone grafting and sinus augmentation. The authors used cortico-cancellous bone blocks from the iliac crest for onlay grafting and a mixture of autologous bone graft and an autologous platelet concentrate obtained from platelet-rich plasma for the sinus lift procedure. The teeth were extracted 4 months after bone augmentation was performed. No increased and accelerated bone resorption was observed.⁹⁸

REGIONAL ODONTODYSPLASIA (FIG. 1.52)

Regional odontodysplasia (RO) is a rare, nonhereditary developmental anomaly affecting dental tissues derived from both the mesoderm and ectoderm. The enamel, dentin, and pulp



FIGURE 1.52: Clinical picture of regional odontodysplasia showing hypoplastic teeth

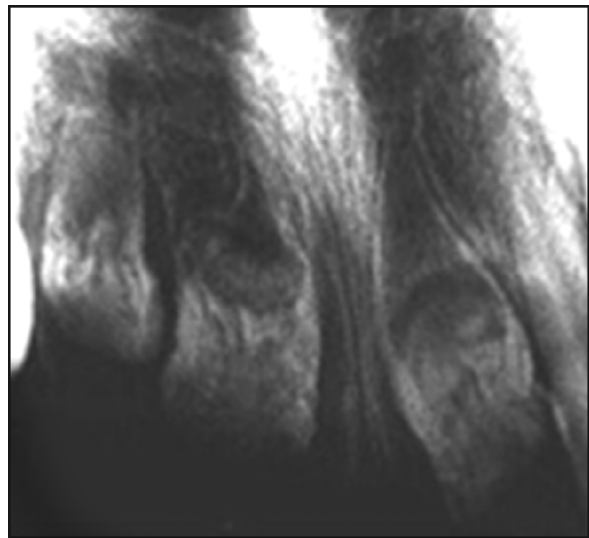


FIGURE 1.53: Radiographic picture of regional odontodysplasia showing ghost like teeth

of teeth are affected, and on radiographs the teeth are described as “ghost teeth” (Fig. 1.53).

The first report of this condition was published by McCall and Wald⁹⁹ in 1947, but the term ‘odontodysplasia’ was introduced by Zegarelli et al¹⁰⁰ in 1963. Since that time, a number of cases have been described under a variety of names; such as localized arrested tooth development, regional odontodysplasia, ghost teeth, odontogenesis imperfecta, unilateral dental malformation, amelogenesis imperfecta non-hereditary segmentalis and familial amelodentinal dysplasia.

Etiology

- Etiology is uncertain but numerous factors have been suggested and considered such as local trauma, irradiation, hypophosphatasia, hypocalcemia, hyperpyrexia.

- Somatic mutation and activation of latent viruses in the odontogenic epithelium have also been linked to the etiology of regional odontodysplasia.
- Presence of nevus, hemangiomas and hydrocephaly have also been associated with regional odontodysplasia but with no definite evidence.

Clinical Features

- Both the primary and permanent dentitions may be affected in the maxilla, mandible or both together. It appears to have a marked preference for the maxilla.
- Generally has a higher prevalence in females.
- Though the condition most often affects only one quadrant, cases with bilateral or multi-quadrant involvement have also been reported. The maxillary teeth are affected more frequently than the mandibular, the maxillary central and lateral incisors and canines being more affected than the posterior teeth.
- In the primary dentition, teeth erupted may be hypoplastic, hypocalcified, with changes in color and form. Affected teeth are likely to be small, brown, grooved and hypoplastic. Gingival tissue can be hyperemic and usually presents a fistula.
- In the permanent dentition, teeth usually are not erupted or can be partially erupted with fibrous gingival tissue and swelling. Root formation may be immature and roots may be aplastic.

Radiographic Features

- There is a lack of contrast between the enamel and dentin, both of which are less radiopaque than their unaffected counterparts.
- Additionally, enamel and dentin layers are thin, giving the teeth a 'ghost-like' appearance.
- The pulp chambers are noticeably enlarged with open apices and enlarged follicles.

Histopathologic Features

- Areas of hypocalcified enamel are visible and enamel prisms appear irregular in direction.
- Coronal dentin is fibrous, consisting of clefts and a reduced number of dentinal tubules; radicular dentin is generally more normal in structure and calcification.
- Irregular dentin with areas of interglobular dentin and presence of immature odontogenic epithelium in the connective tissue.
- Pulpal calcification of various degrees is also commonly seen.
- The mineral content of the affected enamel has been found to be higher than that of dentin in microradiographic studies. The greater density of the enamel is not evident in conventional radiographs, probably because of the thinness of the enamel layer in affected teeth.

Management

1. A continuous and multidisciplinary approach is required for management of the varying clinical problems in regional odontodysplasia.
2. Appropriate restorative procedures, if possible, should be employed to protect the affected erupted teeth.
3. Most clinicians advocate extracting the affected teeth as soon as possible and inserting a prosthetic replacement.
4. Retention of teeth should be an endeavour, particularly in younger children, but if that is not possible, partial dentures may be provided until final rehabilitation with implants and/or fixed prosthesis.
5. Growth of maxillary and mandibular arches should be monitored.

DENTIN HYPOCALCIFICATION

Normal dentin is calcified by deposition of inorganic material in the form of calcium salts. These calcium salts are deposited in the organic matrix in the form of small globules which fuse with each other. But sometimes these globules do not fuse with each other leaving behind interglobular areas of uncalcified matrix. These areas are visible under the microscope. Dentin hypocalcification is caused by similar factors responsible for environmental enamel hypoplasia, e.g. hypoparathyroidism, rickets, etc. Management of this condition is same as that for dentin dysplasia.

DEFECTS OF GROWTH (ERUPTION) OF TEETH

- Premature eruption
- Eruption sequestrum
- Delayed eruption
- Multiple unerupted teeth
- Embedded and impacted teeth
- Ankylosed deciduous teeth

PREMATURE ERUPTION

This has already been discussed under the heading of natal teeth.

ERUPTION SEQUESTRUM

Eruption sequestrum is a small spicule of calcified tissue that is extruded through the alveolar mucosa that overlies an erupting molar or any other tooth in children. This entity was first described by Starkey and Shafer in 1963.¹⁰¹

Etiology

- As the molar teeth erupt through the bone, they will occasionally separate a small osseous fragment from the

surrounding contiguous bone, much in the fashion of a corkscrew.

- In most cases, this fragment probably undergoes total resorption prior to eruption. If the bony spicule is larger or eruption is fast, complete resorption cannot occur and the eruption sequestrum is observed.

Clinical Features

- A small, irregular hard tissue fragment, white in color, with bone-like hardness on the occlusal surface of molars is seen.¹⁰² It is seen just prior to or immediately following the emergence of the tips of the cusps through the oral mucosa.
- The spicule directly overlies the central occlusal fossa but is contained within the soft tissue.
- Chronic inflammatory alterations may also be observed in the gingiva in the area of contact with the osseous tissue.
- As the tooth continues to erupt and the cusps emerge, the fragment of bone completely sequesters through the mucosa and is lost.
- For a few days, the fragment of bone may be seen lying the crest of the ridge in a tiny depression from which it may easily be removed.
- The child may complain of a slight soreness in the area, probably produced by compression of the soft tissue over the spicule during eating and just prior to its breaking through the mucosa.

Radiographic Features

- May be diagnosed before eruption of teeth. It appears as a tiny irregular opacity overlying the central occlusal fossa but separated from the tooth itself.

Histopathologic Features

- Histopathologically, the fragments consist of necrosed cortical bone.
- X-ray microanalyzer findings have revealed the percentages of calcium and phosphorous (by weight) as 78.41 percent and 21.59 percent, respectively, for a calcium to phosphorous ratio of 3.63, which is higher than that seen in normal osseous tissue.

Management

1. No treatment is necessary, since the condition corrects itself.
2. Removal of the spicule may be required.

DELAYED ERUPTION

Delayed tooth eruption is the emergence of a tooth into the oral cavity at a time that deviates significantly from norms established for different races, ethnicities, and sexes.

Etiology

- Delayed eruption of both deciduous and permanent teeth may be due to systemic or local causes.
- The following medical conditions are some of the possible systemic causes of delayed eruption of teeth:
 - Hypothyroidism
 - Hypoparathyroidism
 - Cleidocranial dysostosis
 - Gardner syndrome
 - Vitamin D deficiency
 - Ectodermal dysplasia
 - Pyknodysostosis
 - Deficiency of membrane-type 1 matrix metalloproteinase has been found to be associated with delayed eruption and incomplete root formation.¹⁰³
 - Primary tooth eruption occurs significantly later in children with a birth weight less than 1000 g.¹⁰⁴
 - Hauk et al 2001, found a correlation between the progression of HIV infection to pediatric AIDS and delayed dental eruption and this delay is most closely linked to severity of symptoms and not CD4 depletion.¹⁰⁵
 - The following local causes are also seen to delay eruption of teeth:
 - i. Fibromatosis gingivae
 - ii. Supernumerary teeth
 - iii. Retention of deciduous teeth
 - iv. Crowding of the jaw
- Since the permanent teeth have a wider range of variation in the time of eruption, it is frequently difficult to pinpoint a retardation of eruption.

Management

1. Treatment of the underlying systemic cause may facilitate eruption.
2. Removal of the local factors like fibromatosis or supernumerary teeth helps in alleviating the condition.
3. Recent researches have shown that tooth eruption depends on the presence of osteoclasts to create an eruption pathway through the alveolar bone. Hua F et al, 2007, postulated a new approach that targets osteoclast formation and activation to accelerate the eruption of the affected tooth. These strategies include stimulating osteoclastogenesis by applying the cytokines or small molecules, such as TNF-alpha, IL-1 alpha and MCP-1; triggering osteoclast differentiation by applying molecule associated RANKL signaling, enhancing the function of osteoclasts by applying proteinases, such as CTSK. These molecules can be injected into the oral mucosa of the affected tooth to induce bone resorption, then to rebuild the pathway of tooth eruption.¹⁰⁶

MULTIPLE UNERUPTED TEETH

Multiple unerupted teeth are uncommon without associated local or systemic causes.

Etiology

- Sometimes may be due to a lack of eruptive force, where appearance of teeth and jaws may be normal.
- May be due to local and systemic causes elaborated in the section on delayed eruption.

Clinical Features

- Multiple retained deciduous teeth with delayed eruption of permanent teeth.
- Deciduous teeth may have been shed but the permanent teeth may have failed to erupt. This is often called as “pseudoanodontia”.
- Jaw and appearance of teeth may be normal.

Radiographic Features

Jaw and appearance of teeth may be normal.

Management

1. Treatment of the underlying systemic cause may facilitate eruption.
2. Removal of local factors like fibromatosis or supernumerary teeth help in alleviating the condition.

EMBEDDED AND IMPACTED TEETH

Embedded teeth are those teeth that are unerupted due to a lack of eruptive force.

An impacted tooth results from failure of the tooth to erupt into its normal position because of some physical barrier in the path of eruption.

Secondary retention refers to the cessation of eruption of a tooth after emergence neither because of a physical barrier in the path of eruption nor as a result of an unusual position.

Etiology

- Generally this is an acquired condition but it may be genetic.
- Impaction can be caused by trauma or simply because of the tooth's position in the alveolus so that it is not capable of erupting into its normal position.
- Lack of space due to crowding of the dental arches may result in partial or complete impaction of a tooth.
- Loss of space due to premature loss of a primary tooth and subsequent partial closure of the space may also result in impaction.

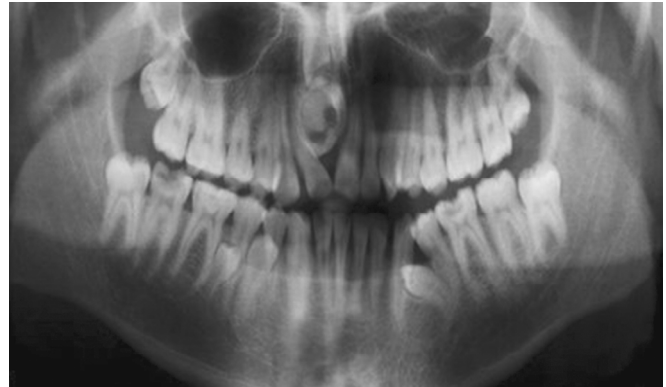


FIGURE 1.54: Radiographic picture of an impacted maxillary right central incisor and mandibular left first premolar

- Not uncommonly, impaction may result due to placement of the tooth in the jaw in a wrong direction. This results in a direction of eruption where the long axis of the tooth is not parallel to a normal eruption path.

Clinical Features

- Impacted and embedded teeth need to be differentiated from missing teeth.
- It is also important to determine whether a tooth is completely or partially impacted. A completely impacted tooth is one which lies completely within the bone and has no communication with the oral cavity. A partially impacted tooth is not completely encased in bone.
- Most commonly impacted teeth are maxillary third molars (22 %), followed by mandibular third molars (18 percent) and maxillary canines (0.9 %) (Fig. 1.54).
- Primary tooth impaction is usually associated with a defect in the development and eruption of the permanent successors.
- Impaction may be mesioangular, distoangular, vertical, horizontal or inverted; all with buccal or lingual deflection.
- At times, the mandibular third molar may be situated completely within the ramus of the mandible.
- Dental caries of an impacted tooth may occur due to a discrete communication of the tooth with the oral cavity.
- A completely embedded or impacted tooth cannot become carious.
- Impaction of permanent maxillary cuspids occurs mainly due to:
 - A long eruption pathway from the place of development to that of eruption.
 - Sequence of eruption in the maxillary arch being first premolar followed by canine followed by second premolar. Hence most of the impactions occur simply due to a lack of space.

- A maxillary cuspid usually points anteriorly and may impinge on roots of the lateral incisors or premolars.
- Periodic pain and trismus may also result due to an impacted tooth.
- A dentigerous cyst may also develop around the coronal portion of an impacted tooth.
- Impacted teeth allowed to remain in situ may occasionally undergo resorption. However, the cause of resorption is not known.
- Cases of ameloblastoma have also been reported to form in the wall of such a cyst.

Management

1. Impacted teeth should be surgically removed or at least monitored on a regular basis.
2. In most cases of the impacted cuspids, a suitable orthodontic appliance may be used to bring the tooth into normal occlusion.
3. Impaction may be avoided by providing a suitable space maintainer in case of premature loss of primary teeth.

ANKYLOSED DECIDUOUS TEETH (FIG. 1.55)

Ankylosis in this context means the fusion of dental hard tissue, cement and dentine with alveolar bone accompanied by loss of soft tissue. In most cases, however, it does not involve the whole periodontal ligament; single bone bridges in the periodontal ligament suffice to disturb the normal vertical development of the tooth in comparison to its unaffected neighbouring teeth. As long as the vertical discrepancy of single or even all deciduous teeth does not exceed 2 to 3 mm, there is no clinical relevance. But if a deciduous tooth reoccludes into bony structure up to the level or even below the gingiva,



FIGURE 1.55: Clinical picture of an ankylosed tooth submerged below the occlusal plane

the successor is always involved. The terms submerged teeth and infraocclusion applied to this condition are inaccurate. Henderson, 1979, pointed that ankylosis should be considered an interruption in the rhythm of eruption.¹⁰⁷

Etiology

Etiology of this entity is unknown but three hypotheses have been put forth:

1. Familial pattern, probably non-sex linked trait.
2. Intermittent resorption and repair during the routine exfoliation process of the deciduous tooth.
3. A relationship between congenital absence of permanent teeth and ankylosed primary teeth has been suggested.

Clinical Features

- The lower second deciduous molars are affected most frequently; in the permanent dentition a single or all first molars may show signs of ankylosis. If more permanent teeth of the buccal segment are affected, this is defined as a general disturbance of the periodontal tissue.
- Ankylosis of primary anterior teeth is a rare phenomenon and occurs following trauma. Alexander et al 1980, reported an unusual case of ankylosis of multiple primary molars where all the primary molars were ankylosed to the alveolar bone.¹⁰⁸
- Usually, ankylosis of the primary molar occurs only after its root resorption begins.
- If ankylosis occurs early, eruption of adjacent teeth may progress enough that the ankylosed tooth is far below the normal plane of occlusion and may even be partially covered with soft tissue.
- However, an epithelium lined tract will extend from the oral cavity to the tooth.
- Ankylosis may occasionally occur even before the eruption and complete root formation of the primary tooth.
- The ankylosed tooth will have a solid sound when tapped upon with a blunt instrument whereas the normal tooth will have a cushioned sound due to an intact periodontal membrane which absorbs some of the shock of the blow. This test aids in clinical diagnosis of the ankylosed tooth.

Radiographic Features

A break in the continuity of the periodontal membrane indicates an area of ankylosis.

Management

1. Early recognition and diagnosis are extremely important.
2. Treatment may involve surgical removal, but if the ankylosed tooth poses no space problems in the arch

and is not involved by caries, it may be kept under observation. It is quite likely that the ankylosed tooth would undergo root resorption and normal exfoliation sometime later.

3. The prognosis for active elongation of ankylosed teeth is uncertain or poor.

FISSURAL CYSTS OF THE ORAL REGION

- Nasopalatine duct cyst
- Median palatal cyst
- Globulomaxillary cyst
- Median mandibular cyst
- Nasoalveolar cyst
- Palatal and alveolar cysts of newborns
- Thyroglossal tract cyst
- Epidermal inclusion cyst
- Dermoid cyst
- Heterotopic oral gastrointestinal cyst

NASOPALATINE DUCT CYST

The nasopalatine duct cyst (NPDC) is a developmental, non-neoplastic cyst that is considered to be the most common of the nonodontogenic cysts. NPDC is one of many pathologic processes that may occur within the jawbones, but it is unique in that it develops in only a single location, which is the midline anterior maxilla (Fig. 1.56).

Etiopathogenesis

The development of the face and the oral cavity takes place between the fourth and eighth weeks of intrauterine life. The secondary palate is formed during the eighth and twelfth weeks. In the midline between the primary and secondary palates, two

channels (the incisive canals) persist. The palatine processes probably partly overgrow the primary palate on either side of the nasal septum. Thus, the incisive canals represent passageways in the hard palate, which extend downward and forward from the nasal cavity. Just before exiting the bony surface of the hard palate (incisive foramen or incisive fossa), the paired incisive canals usually fuse to form a common canal in a Y shape.

The fusion of facial processes in the embryologic development of the maxilla results in the formation of a pair of epithelial strands (the nasopalatine ducts) that traverse the incisive canals downward and forward, connecting the nasal and oral cavities. The nasopalatine duct leads from the incisive fossa in the oral cavity to the nasal floor, in which it ends in the nasopalatine infundibulum.

The types of epithelia that line the nasopalatine duct are highly variable, depending on the relative proximity of the nasal and oral cavities. The most superior part of the duct is characterized by a respiratory-type epithelial lining. Moving downward, the lining changes to cuboidal epithelium. In the most inferior portion closest to the oral cavity, squamous epithelium is usually present. In addition to the nasopalatine ducts, branches of the descending palatine and sphenopalatine arteries, the nasopalatine nerve, and mucus-secreting glands are present within the incisive canals.

The nasopalatine ducts ordinarily undergo progressive degeneration; however, the persistence of epithelial remnants may later become the source of epithelia that gives rise to NPDC, from either spontaneous proliferation or proliferation following trauma (e.g. removable dentures), bacterial infection, or mucous retention. Genetic factors have also been suggested. The mucous glands present among the proliferating epithelium can contribute to secondary cyst formation by secreting mucin within the enclosed structure. NPDC can form within the incisive canal, which is located in the palatine bone and behind the alveolar process of the maxillary central incisors, or in the soft tissue of the palate that overlies the foramen, called the cyst of the incisive papilla.

Clinical Features

- Males are affected 1.8 to 20 times more often than females.¹⁰⁹
- NPDCs occur over a wide age range (7 to 88 years) and they also occur in fetuses.¹¹⁰ Most patients who are affected are aged 30 to 60 years.
- Large and more destructive cysts that have perforated the labial and palatal bony plates may present as expansile, fluctuant swellings of the anterior palate and the posterior palate.
- Extrabony cysts that develop within the soft tissues of the incisive papilla area of the anterior hard palate (called the

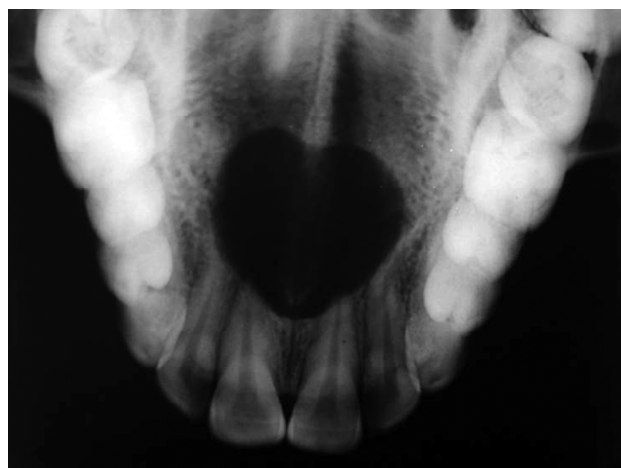


FIGURE 1.56: Radiographic picture of nasopalatine duct cyst showing radiolucent area in the palate

cyst of the incisive papilla) may present as a translucent or bluish colored, dome-shaped swelling. The clinically apparent discoloration is due to accumulation of fluid contents within the cyst.

- NPDCs clinically demonstrate slow and progressive growth, sometimes exceeding 60 mm in diameter.
- Tooth displacement is a common finding, having been reported to occur in 78 percent of patients, whereas bony expansion is noted in only 1.4 percent of patients.¹¹¹

Management

1. NPDCs are treated by enucleation via a palatine or buccal approach.
2. Recurrence is uncommon, having been reported in 0 to 11 percent of patients.¹¹² If components of the long sphenopalatine nerve are removed during surgery, it may cause paresthesia to the anterior palate.
3. Complete bone regeneration within the bony defect is expected postoperatively.

MEDIAN PALATAL CYST

Median palatal cyst is an epithelium lined sac containing fluid, present in the midline of the hard palate, between the lateral palatal processes.

Etiology

It is of developmental origin.

Clinical Features

- It is asymptomatic and discovered incidentally during routine dental or radiological examination.
- Its occurrence is rare.
- A swelling on the oral surface of the hard palate is generally seen.
- Rarely, it may cause elevation of the nasal floor and nasal obstruction.

Radiographic Features

It appears as a radiolucent area in the midline of the palate.

Histopathologic Features

- The cyst consists of a dense fibrous connective tissue lined by stratified squamous epithelium.
- The connective tissue consists of chronic inflammatory cell infiltrate.
- Some of the cystic lining shows pseudostratified ciliated columnar epithelium.

Management

Treatment includes surgical excision and thorough curettage.

GLOBULOMAXILLARY CYST

The globulomaxillary cyst is a cyst that appears between a maxillary lateral incisor and the adjacent canine. It was first described by Thoma as a developmental (fissural) cyst.

It is present within the maxilla at the junction of the globular portion of the medial nasal process and the maxillary process.

Etiology

It is thought to be a developmental fissural cyst arising in the area between the nasal process and maxillary process. It is now believed that all these lesions are actually other odontogenic cysts, such as odontogenic keratocysts or lateral periodontal cysts. In fact, it is now recommended that this entity should be used only as a clinically descriptive term.

Clinical Features

- Found between the maxillary lateral incisor and the adjacent canine.
- All regional teeth are found to be vital.
- It may often cause the roots of adjacent teeth to diverge.
- This cyst should not be confused with a nasopalatine cyst.
- The lesion is usually discovered during routine dental examination.
- It is asymptomatic, but becomes slightly tender if infected.
- Bilateral lesions are reported, but rarely.

Radiographic Features

- It appears as an oval, round or “inverted pear-shaped radiolucency” on radiographs.
- According to Wysocki,¹¹³ the majority of the lesions (over 80 percent) presenting with the radiographic features of a globulomaxillary cyst are of periapical origin.

Histopathologic Features

- Histologically, it can be a variety of odontogenic lesions predominantly of periapical origin, i.e. periapical cyst and granuloma, odontogenic keratocyst, or more rarely odontogenic myxoma, squamous odontogenic tumor, adenomatoid odontogenic tumor or central giant cell granuloma (the latter is not of tooth origin). However, evidence in literature is in favor of this lesion being predominantly of tooth origin.
- Histologic features will usually not be supportive of a periapical lesion.



FIGURE 1.57: Radiographic picture of median mandibular cyst

Management

Treatment is by enucleation, or surgical removal.

MEDIAN MANDIBULAR CYST (FIG. 1.57)

It is a soft tissue sac which develops in the mouth near the middle of the lower jaw in conjunction with normal growth or as the result of an odontogenic cyst.

Etiology

Two schools of thoughts have been put forth for the origin of this cyst

1. Some researchers suggest the origin of this cyst from proliferation of epithelial remnants entrapped in the median mandibular fissure during the fusion of mandibular arches.
2. Cyst may originate from supernumerary enamel organ in the anterior mandibular segment.

Clinical Features

- They are often asymptomatic and diagnosed during routine radiographic examination.
- They produce expansion of cortical plates.

Radiographic Features

It appears either as a unilocular or multilocular well-circumscribed radiolucent lesion.

Histopathologic Features

The cyst is lined by stratified squamous epithelium showing numerous papillary projections.

Management

Treatment is by conservative surgical excision.

NASOALVEOLAR CYST

Nasoalveolar cyst is a fissural cyst arising outside the bones at the junction of the globular portion of the medial nasal process, lateral nasal process, and maxillary process.

Etiology

- It is formed as a result of proliferation of entrapped epithelium along the fusion line of the globular portion of the medial nasal process, lateral nasal process, and maxillary process.
- Roed-Peterson,¹¹⁴ 1969, and Christ,¹¹⁵ 1970, suggested that the cyst originates from the lower anterior part of the naso-lacrimal duct, rather than the entrapment of epithelium.

Clinical Features

- Most commonly seen in females.
- Incidence of occurrence ranges from 12 to 75 years of age.
- Causes a swelling in the mucolabial fold and floor of the nose.

Histopathologic Features

The cyst is lined by pseudostratified or stratified ciliated columnar epithelium containing goblet cells (Fig. 1.58).

Management

Treatment is by surgical excision.

The following have been discussed in the section on cysts in the pediatric population:

- Palatal and alveolar cysts of newborns
- Thyroglossal tract cyst
- Epidermal inclusion cyst
- Dermoid cyst

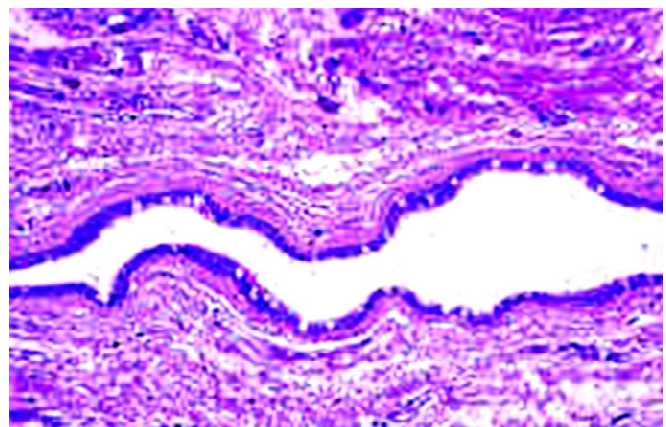


FIGURE 1.58: Histopathologic picture of nasoalveolar cyst showing stratified ciliated columnar epithelium containing goblet cells

Heterotopic oral gastrointestinal cyst is generally not seen in the pediatric population, hence does not warrant explanation in this textbook.

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Caries in Children

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CHAPTER OVERVIEW

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Caries susceptibility and caries activity

Caries activity tests
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Caries assessment tool
Caries risk assessment
Prevention of caries
Management of caries:
 Remineralization of early lesions
 Restoration
Pulp treatment:
 Indirect pulp capping
 Direct pulp capping
 Partial pulpotomy in permanent teeth
 Vital pulpotomy
 Non-vital pulpotomy
 Partial pulpectomy in permanent teeth
 Pulpectomy in primary teeth

INTRODUCTION

Epidemiologically, caries has become a dichotomous disease in children in most developed countries: 50 percent of the children are caries free whereas 20 percent of them account for 75 percent of the lesions. This indicates a dramatic change in the pattern of disease. Bowen, 1997, stated that while there is a decline in caries prevalence, it is clear that dental caries still remains the most prevalent disease afflicting humans.¹

Hence, a continued updating on the etiologic, preventive and management aspects of caries is required to develop an appropriate response to the current changes in patterns of disease.

Dental caries is known to be a multifactorial disease. It should be learned, not as small parts of individual subjects, but as a subject of cariology including the biochemistry, nutrition, oral pathology, oral microbiology, preventive dentistry, public health dentistry, pedodontics and operative dentistry aspects.

DEFINITION

- A histopathologist may define caries in terms of the stages of the lesion viewed microscopically
- A chemist may describe the process in terms of the inter-relationship between pH, mineral flux and solubility at the tooth-saliva interface
- A microbiologist on the other hand may define caries in terms of interactions involving oral bacteria and the dental tissues
- Thus dental caries is a multifactorial disease, which is the result of interaction between the tooth (host) and the environment around it including the bacteria, saliva and diet of an individual with the time factor playing a significant role
- Derived from Latin word for rot or decay
- Greek word 'Ker' meaning death
- **Shafer, 2007**, defines dental caries as an irreversible microbial disease of the calcified tissues of the teeth,

characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitation.²

- **Newbrun, 1989**, defines dental caries as a pathological process of localized destruction of tooth tissues by microorganisms.³
- **Ostrom, 1980**, defines dental caries as a process of enamel or dentin destruction that is caused by microbial action at the tooth surface and is mediated by physiochemical flow of water dissolved ions.
- **Hume, 1993**, defines dental caries as essentially a progressive loss by acid dissolution of the apatite mineral component of the enamel then the dentin, or of the cementum then dentin.
- **Pinkham, 2005**, defines dental caries as a dietary carbohydrate-modified infectious disease in which saliva functions as a critical regulator.⁴

HISTORY

- First evident in Homosapiens since paleolithic times
- von Leeuwenhoek observed that dolichocephalic skulls of men from preneolithic periods showed no caries
- Skulls from brachycephalic men showed carious teeth
- No carious lesions were seen in the Pithecanthropus men

- Fairly extensive decay was seen in one skull of a Rhodesian man from Neanderthal age
- About one half of 24 skulls of prehistoric race from central Europe 15,000 years ago showed dental caries
- Lots of studies demonstrate that populations which have not acquired dietary habits of modern, industrialized man have relative freedom from dental caries
- Prevalence of dental caries was low in Australian aborigines, New Zealand Maoris, Eskimos, Ghanaians, tristan da Cunhans and Bantu tribes of South Africa prior to exposure to European diet.

TRENDS IN CARIES EPIDEMIOLOGY

See Table 2.1.

EARLY THEORIES OF DENTAL CARIES⁵

WORM THEORY

- According to ancient Sumerian texts, toothache was caused by worms that drank the blood of the teeth and fed on the roots of the jaws
- Clay tablets have been discovered from the Mesopotamian area dated 5000 BC engraved with the legend of the worm.

TABLE 2.1: Epidemiology of dental caries

Sr. No.	Investigators	Year	Place	Age group (years)	No. of Children	Prevalence	DMFT/deft
1.	Kokila	1951	Gujarat	3-15			12.60
2.	Chaudhary and Chawla	1957		5-16	2991		1.9/11.1
3.	Miglani and Sharma	1963		15-25	1125		5.0
4.	Tiwari and Chawla	1977	Chandigarh	6-16	1511		3.93
5.	Brunelle and Carlos	1987	Bethesda, Maryland	5-17		50%	
6.	Holt	2001	Greater Manchester	3-4	762		1.4
7.	Pankaj et al	2002-03	Delhi (urban) (rural)	5-6			1.3 1.1
8.	Rawalani et al	2002-03	Wardha	12			3.8
9.	Pankaj et al	2002-03	Delhi (urban) (rural)	15			1.7 1.5
10.	Jose and King	2003	Kerala	8-48 months (mean=2.5)		44%	1.84
11.	Mahesh	2005	Chennai	5-6			3.51
12.	Hegde et al	2005	Belgaum	12			2.41
13.	Goyal A et al	2007	Chandigarh	6 9 12 15			4.0 4.61 3.03 3.82
14.	Livny et al	2007	Jerusalem	1-3	102	17.6%	

- Oracle bones from the Shang dynasty dated before 1000 BC bear the Chinese character for caries depicting the worm invading the mouth
- This theory was earlier universally believed including China, India, Finland, Scotland, etc
- Guy de Cahuliac (1300-1368), surgeon, advocated fumigation with seeds of leek, onion and hyoscyamus
- Fumigation was also used by the Chinese, Egyptians and British in the 19th century
- Antony von Leeuwenhoek (1700), 'father of modern microscopy', described little worms "taken out of a corrupt tooth" and said that they caused the pain in toothache
- Shakespeare has also mentioned worms in a tooth in his famous play "Much Ado about Nothing"
- Japanese: *Mush-ha*=hollow teeth, carious teeth. The Chinese also follow similar terminology.
- Ficinus, 1847, noticed filamentous organisms called denticolae in carious material, which he thought were responsible for decomposition of teeth
- Orland and Fitzgerald, Jordan and Acharid emphasized that caries cannot occur without microorganisms
- Dubois, 1954, stated that microorganisms had a toxic effect on tooth tissue which led to its breakdown
- Antony von Leeuwenhoek, from early observations of scrapings, suggested that caries is a microbial process.

CHEMOPARASITIC THEORY

- This is a blend of two theories and finds the maximum favor among the researchers
- Willoughby D Miller, 1890, has been credited with this theory, but tremendous work was done by Pasteur and Emil Magitot before him
- Pasteur discovered that microorganisms transform sugars to lactic acid in the process of fermentation
- Emil Magitot, 1867, demonstrated that fermentation of sugars caused dissolution of tooth *in vitro*
- Berlin, Leber and Rottenstein, 1867, implicated bacteria as the causative agent, as they observed *Leptothrix buccalis* in dentinal tubules of carious teeth
- Underwood and Miles, 1881, observed micrococci, oval and round bacteria in histological sections of carious teeth.
- Miller learned methods of isolating and staining in Koch's laboratory and demonstrated the following facts in a series of experiments:
 - Acid was present within the deeper carious lesion as shown by reaction to litmus paper.

HUMORS

- According to the ancient Greeks, there are four elemental fluids—blood, phlegm, black bile, yellow bile. Thus the four humors—sanguine, phlegmatic, melancholic, choleric. Any imbalance in these causes disease
- Galen, a Greek physician, suggested that it was this internal action of acid and corroding humors that caused caries
- Hippocrates accepted the prevailing Greek philosophy but also drew attention to stagnation of food resulting in caries
- Aristotle mentioned that soft sweet figs putrefied and produced damage to the teeth.

VITAL THEORY

- This theory regarded caries as originating within the tooth itself analogous to bone gangrene
- This theory was proposed at the end of the 18th century and remained dominant till the middle of the 19th century
- Caries is known to have extensive penetration into the dentin with a barely detectable catch in the fissure; hence the support for this theory.

CHEMICAL THEORY

- Parmly, 1819, rebelled against the vital theory. He suggested that a 'chymical agent' is responsible for caries.
- Robertson, 1835 and Regnart, 1938, carried out experiments and showed that different dilutions of inorganic acids corroded enamel and dentin.

PARASITIC OR SEPTIC THEORY

- Erdl, 1843, described filamentous parasites in the 'surface membrane' of teeth

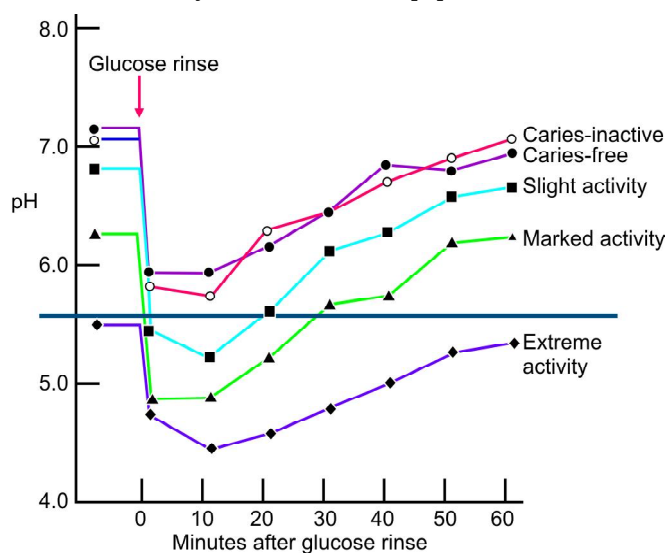


FIGURE 2.1: Stephen's curve. A plot of the pH of plaque before and after a glucose mouth rinse. (After Stephan and Miller, 1943)

- Different kinds of foods (bread, sugar, but not meat) mixed with saliva and incubated at 37°C could decalcify the entire crown of a tooth
- Several types of mouth bacteria (at least 30 species were isolated) could produce enough acid to produce dental caries
- Lactic acid was an identifiable product in carbohydrate-saliva incubation mixtures
- Different microorganisms (filamentous, long and short bacilli and micrococci) invade carious dentin.
- Williams, 1897, observed that plaque on enamel surfaces localizes organic acids and prevents their dilution and neutralization by saliva.
- Rapid growth of *S. mutans* lactate major end product
- Slow growth of *S. mutans* volatile fatty acids predominate
- Other metabolic processes within plaque (Fig. 2.5):
 - L-amino acid $\xrightarrow{\text{decarboxylase}}$ amine CO_2
 - $\text{RCHNH}_2\text{COOH} + 0.5 \text{O}_2 \xrightarrow{\text{directly}} \text{RCO}_2\text{COOH} + \text{NH}_3$
L-amino acid -keto acid

Evaluation

Drop in pH

- Amount and duration of the drop in pH is influenced by:
 - Amount of interdental plaque
 - Predominant flora
 - Rate of salivary flow
 - Type of concentration of substrate
 - Location of the plaque
- Lactic, acetic, propionic, formic and butyric acids have been identified in plaque (Figs 2.3 and 2.4)
- Plaque consists of both homo and heterofermentative organisms
- *S. mutans* is homofermentative, i.e. 90 percent lactic acid is formed alongwith other acids, CO_2 , ethyl alcohol
- Actinomyces can be both homo- and heterofermentative depending on the environment (Fig. 2.2)
- Veillonella, peptostreptococci, arachnia and propionibacteria on fermentation produce propionic acid.
- Neisseria produces acetate by utilizing glucose, pyruvate and lactate.

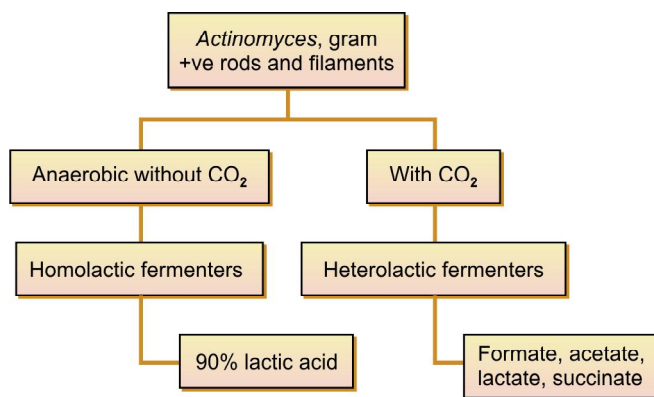


FIGURE 2.2: Schematic representation of acid formation by micro-organisms (actinomyces as responsible for dental caries)

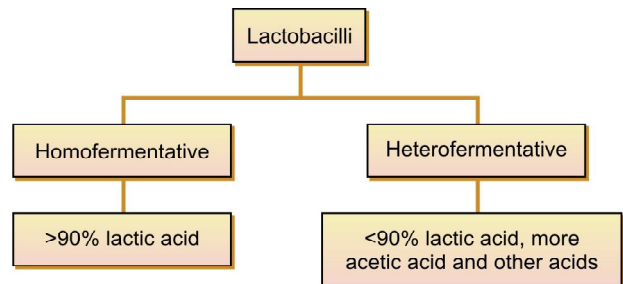


FIGURE 2.3: Schematic representation of acid formation by micro-organisms (lactobacilli) responsible for dental caries

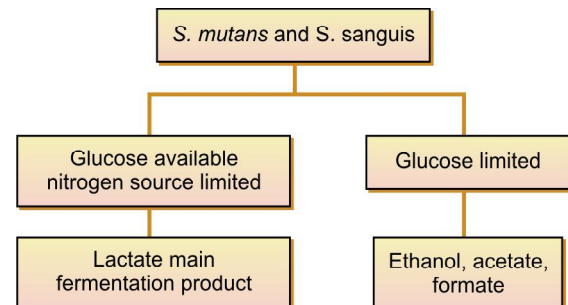


FIGURE 2.4: Schematic representation of acid formation by micro-organisms (*S. mutans* and *S. sanguis*) responsible for dental caries

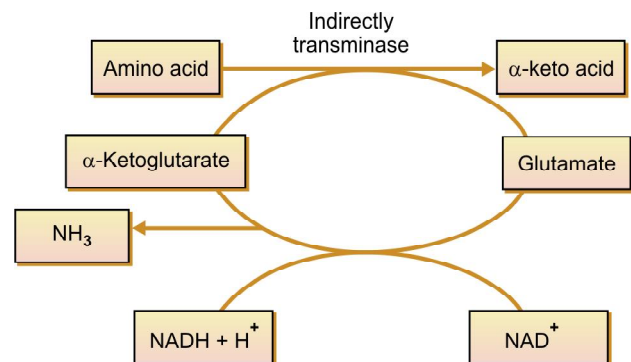
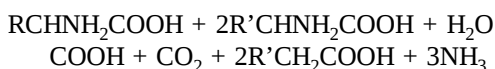


FIGURE 2.5: Schematic representation of formation of -keto acid as one of the metabolic processes within plaque

In anaerobic bacteria, the Strickland reaction forms ammonia as follows:



Stephen's Curve (Fig. 2.1), outlining the drop in pH after a glucose rinse in persons with varied caries activity has formed the basis of understanding the role of glucose in caries since decades.

Thus, the chemoparasitic theory remains the most widely accepted, with newer experiments throwing more light on the intricate biomechanisms of caries.

PROTEOLYTIC THEORY

- The human tooth consists of only 1.5 to 2 percent organic material
- **According to Gottlieb, 1944**, the initial action on the tooth was due to proteolytic enzymes attacking the lamellae, rod sheaths, tufts and walls of the dentinal tubules
- He based these observations on histological specimens and the similarity between carious enamel and enamel whose organic components were stained with silver nitrate
- **Frisbie, 1944**, described caries as proteolytic involving depolymerization and liquefaction of the organic matrix of enamel
- **Pincus, 1949**, contended that the proteolytic organisms attacked the protein elements initially, then prism sheaths were destroyed and the loosened prisms fell out. He also suggested that sulfatases of Gram negative bacilli hydrolyzed "mucoitin sulfate" of enamel or chondroitin sulfate of dentin and produced sulfuric acid.

Evaluation

- **Gottlieb, Frisbie and Pincus** were all histologists, who observed slides and assumed a mechanism of action of the organisms, which are biochemical events. However, in early enamel lesions, there is an actual increase in organic matter
- Also, nonproteolytic bacteria have also been known to cause extensive cavitation
- No experimental support was obtained for this contention.

PROTEOLYSIS—CHELATION THEORY

- **Schatz and Martin, 1955**, challenged the chemoparasitic theory and advocated the proteolysis—chelation theory stating that acid may actually prevent tooth decay by interfering with growth and activity of proteolytic bacteria thus protecting the enamel organic matter
- Greek *chele* = claw. A chelating agent is a molecule capable of seizing and holding a metal ion in a claw like grip and forming a heterocyclic ring. Well known chelates in biology

include hemoglobin (containing iron), chlorophyll (containing magnesium), vitamin B₁₂ (containing cobalt), etc

- Chelation has been proposed as an explanation for tooth decay, whereby the inorganic components of enamel can be removed at a neutral or alkaline pH
- The initial attack is on the organic components of enamel, whose breakdown products have chelating properties and thereby dissolve the minerals in the enamel
- **March et al, 1971**, proposed the hypothesis that demineralization is initiated at acid pH and continued by complex-forming agents when the pH of plaque is neutral.

Evaluation

- Although chelators are present in plaque and saliva, it is not clear whether they are present in sufficient quantity.
- Amount of calcium removed as an ionic salt v/s calcium chelate complex is also not clear.
- **Zipkin, 1953 and Larson and her associates, 1959**, performed animal studies with EDTA in the cariogenic diet and showed that it resulted in an increase in the severity of dental caries as well as a difference in the distribution pattern of lesions.

SUCROSE—CHELATION THEORY

- Also called as the phosphate sequestration theory.
- **Eggers-Lura, 1967**, suggested that sucrose itself and not the acid derived from it can cause dissolution of the tooth by forming an ionized calcium saccharate. Calcium saccharates and calcium complexing products require inorganic phosphate, which is subsequently removed from the enamel by phosphorylating enzymes.
- **Luoma, 1964**, suggested that since bacteria require phosphate, inorganic phosphate from the tooth is taken up by plaque bacteria.

Evaluation

- Saliva itself is an abundant source of inorganic phosphates, hence it is highly unlikely that microorganisms would remove complex phosphates from the tooth, rather than the easily available ones.
- Reinvestigation failed to confirm the theory.
- Soluble complexes between sucrose and calcium oxide and between sucrose and calcium hydroxide can be formed even at an alkaline pH, although not with calcium phosphate.

AUTOIMMUNE THEORY

- **Burch and Jackson, 1966**, based on their epidemiologic studies, suggested that genes determine whether a site on a tooth is at risk or not.

Evaluation

- **Jenkins, 1961**, argued that the data is purely epidemiologic.⁶
- Four studies state that there is a statistically significant genetic component in susceptibility to caries.
- Evidence of a genetic contribution to caries was based on four questions as a part of a questionnaire:
 - Altered dental hard tissue
 - Immune response
 - Dietary consumption of sugar
 - Saliva
- **Bachrach and Young, 1927**, examined 301 pairs of twins of which 130 were monozygotic and 171 dizygotic.⁷
- 93 were same sex dizygotic and 78 were different sex dizygotic.
- They proved that heredity plays a subsidiary part in inheritance of caries.
- **Goldberg, 1930**, reported that identical twins showed decay in corresponding teeth.⁸
- Few investigators state that heredity affects only the shape of a tooth, its pits and fissures, its position in the dental arch.
- Caries experience of monozygotic twins had greater concordance.
- **Mansbridge, 1959**, observed 224 pairs of twins and suggested that environmental factors had a greater influence on development of caries.⁹
- Comparison between pit and fissure and smooth surface caries was also done, but equal genetic weight cannot be ascribed to both.
- DMF difference between twins was most dramatic for smooth surface caries on anterior teeth.

Genetic modification of dental enamel was also examined:

- Highly defined clinical phenotype to identify the altered biomineralized matrix protein and to begin to search the genome for linkage to a precise change in DNA sequence was delineated
- Epidermolysis bullosa (EB) has been shown to have both an alteration in the enamel and an increased caries incidence
- The mutations in EB result in four different forms of the disease: Recessive dystrophic, Dominant dystrophic, Junctionalis and the Simplex types
- Wright examined 252 patients of EB-junctionalis and EB-recessive dystrophic. Both were associated with an increased incidence of dental caries
- Junctionalis form showed altered chemical composition of the enamel, whereas recessive dystrophic form does not exhibit altered enamel

- In EB-junctionalis, enamel has greater porosity and thus increased surface area for the effects of acids generated by cariogenic bacteria
- Enamel contains large amounts of serum albumin that inhibits crystal formation and thus remineralization of altered sites
- Genetic origin for EB-junctionalis has been linked to one of three different genes: laminin 5, $\alpha 4$ -integrin and Type XVII collagen
- All have the potential to alter the relationship of the ameloblast to the developing enamel extracellular matrix and thus lead to a primary defect in the enamel hard tissue.

Genetic modification of immune response

- Inherited or acquired immune deficiency subjects an individual to increased risks for and incidence of dental caries.
- Specific immune complex molecules for association with increased risk for caries have been identified.
- **Lehner et al, 1981**, examined 24 individuals and found that HLA DRw6-1, 2, 3 had a significant relationship to the DMFS index and to low dose response to Streptococci mutans antigens.¹⁰
- HLA-DR4 was found to have no association.
- de Vries, 1985, reported no association between HLA-DR types and caries incidence.¹¹
- Studies by **Senpuku, 1998¹²** and **Acton, 1999,¹³** correlated specific HLA DR types with binding S. mutans antigens and S. mutans colonization.
- Acton concluded that “genes within MHC modulate the level of oral cariogenic organisms”.

Inherited alterations in sugar metabolism

- There is a paradoxical relationship between sensitivity to sweet taste and caries incidence
- Hereditary fructose intolerance is a condition which results in low caries incidence
- Inherited defects in sugar metabolism would most likely alter substrate availability in a manner identical to any other dietary restriction and not by a genetically unique mechanism.

Genetic regulation of salivary gland function

Xerostomia is associated with dramatically increased rates of dental caries.

NUTRITIONAL DEFICIENCY THEORY

Insufficient phosphate intake and improper dietary calcium-to-phosphate ratio may contribute to the development of caries.

Evaluation

No experimental support.

BACTERIAL ALKALINE PHOSPHATASE THEORY

It was suggested that bacterial alkaline phosphatase was found to release phosphate from enamel *in vitro*, thus participating in caries destruction by acting on phosphoproteins of enamel.

Evaluation

- Commercial enzyme preparation was utilized and it was observed that ammonium sulfate itself can release phosphate from teeth in the absence of bacteria
- Alkaline phosphatase is an intracellular enzyme. Hence lysis of the cells would have to occur to free the enzyme.

CURRENT CONCEPTS IN CARIES ETIOLOGY

Keyes' triad given in 1960 (Fig. 2.6):¹⁴

- Interplay of three principle factors:
 1. The host (saliva and teeth)
 2. The microflora
 3. The substrate or diet
- In addition, a fourth factor *time* must be considered. Hence, it is now considered to be a tetrad (**Newbrun, 1982**) (Fig. 2.7).¹⁴

HOST FACTORS: SALIVA

- It is a mixture of secretions in the oral cavity, mostly from the major and minor salivary glands
- Xerostomia: (*xeros* = dry; *stoma* = mouth)
- First described by **Bartley in 1868**
- Xerostomia has been explained in detail in the section on Salivary gland lesions in children.

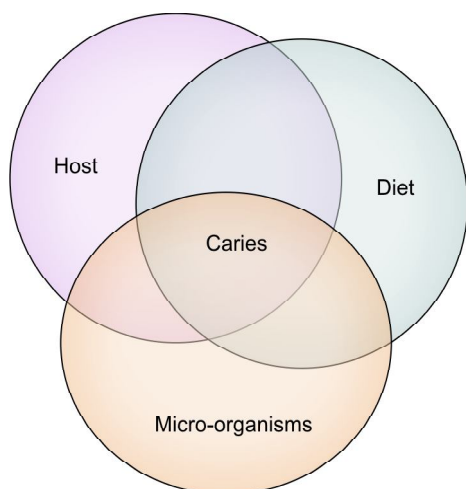


FIGURE 2.6: Schematic representation of Keyes' triad

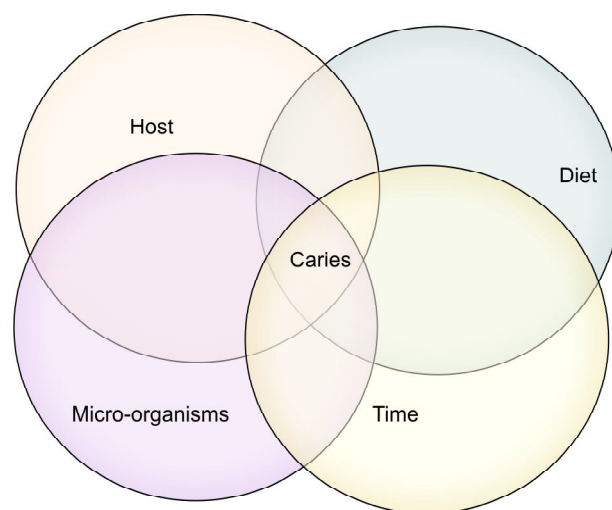


FIGURE 2.7: Schematic representation of factors of tetrad (Newbrun, 1982)¹⁴

Etiology

- Sjögren's syndrome
- Therapeutic radiation
- Surgical removal of salivary glands
- Chronic administration of anticholinergic drugs
- Congenital absence or malformation
- Anxiety, mental stress and depression

Alterations in the Oral Cavity Due to Xerostomia

- Longer eating (modification of eating habits to compensate decreased salivary flow)
- Greater food retention
- Possible alterations in bacterial flora of the mouth
- Decreased mineralization of enamel

Management

Management of patients with xerostomia is based on symptomatic treatment:

- Fluoride therapy
- Dietary control
- Oral hygiene
- Avoidance of xerostomic drugs
- Use of artificial saliva (Orex saliva substitutes, xero-lube) (Table 2.2)

Salivary Composition and its Relation to Caries

Salivary buffers

- Buffer is a solution that tends to maintain a constant pH
- In saliva, the chief buffer systems are bicarbonate-carbonic acid and phosphate, of which bicarbonate is the most important salivary buffer due to the following factors:
 - It can buffer rapidly by losing carbon dioxide

TABLE 2.2: Components of various saliva substitutes

Ingredients	Category
Salt	NaCl, KCl, CaCl ₂ , MgCl ₂ , etc.
Lubricant	Carboxymethyl cellulose, animal mucins, glycerin
Sweetener	Sorbitol, xylitol
Flavor	Mint, wintergreen, coriander-spice, lemon
Preservative	Methyl p-hydroxybenzoate, paraben
Color	FDC Red Dye No. 40
Therapeutic	NaF

- Its pK is close to that encountered in plaque, and therefore, it is more effective in that range
- As the flow rate increases, the bicarbonate concentration increases rapidly, whereas phosphate falls slightly with increased flow rate
- After removal of bicarbonate, the buffering capacity of saliva is markedly reduced.
- Urea is continuously secreted in saliva. Plaque microorganisms can convert urea to other nitrogenous products and ammonia. This ammonia, thus formed can also act as a buffer
- Longitudinal studies have proved that patients having higher buffer capacity tend to have less caries
- **Critical pH:** it is not a particular value, but a concept wherein it can be considered as the pH at which any particular saliva ceases to be saturated with calcium and phosphate. Hence, below this value, the inorganic material of a tooth may dissolve
- It varies according to the calcium and phosphate concentration but is usually about 5.5 for hydroxyapatite and 4.5 for fluorhydroxyapatite.

Antibacterial factors in saliva

- Lysozyme:
 - Found in saliva, tears, egg white, tissues and body fluids
 - Hydrolytic enzyme which acts on cell wall peptidoglycans of bacteria and lyses many cariogenic and noncariogenic streptococci
- Salivary peroxidase and thiocyanate ion:
 - Acts on hydrogen peroxide generated by certain bacteria
 - The oxidation reaction can inactivate various enzymes of glycolytic pathway and thereby temporarily inhibit the growth, respiration and metabolism of most species of oral bacteria.

HOST FACTORS: IMMUNIZATION (CARIES VACCINE)

- Humans are blessed with humoral and cellular immunity.
- Studies on immunity against caries include the following:

- Animal studies
 - i. Local immunity (direct stimulation of sIgA)
 - ii. Oral immunization (indirect stimulation of sIgA)
 - iii. Stimulation of serum antibodies
- Human studies
 - i. Secretory IgA
 - ii. Serum antibodies
- Passive immunity
- Outlook towards caries immunization
- Modern techniques of genetic bioengineering

Animal Studies

- Animal studies involve active immunization against *streptococcus mutans* done with the help of antigens derived from killed *S. mutans*, cell extracts, cell free culture fluid and glucosyltransferase (GTF)
- Complete Freund's Adjuvant (CFA) may also be used.

Local immunity

- Rodents were immunized by repeated injections near the parotid and submandibular glands with the vaccines prepared from *S. mutans* (either killed cells or GTF)
- Salivary IgA was formed that agglutinated *S. mutans* or inhibited glucans synthesis
- Greater reduction of caries on smooth surfaces than occlusal surfaces was observed.

Oral immunization (Fig. 2.8)

- Peyer's patches in the gut associated lymphoid tissues contain B cells that populate the lamina propria of the gastrointestinal tract and become IgA producing plasma cells. These cells migrate to local sites and the antigen sensitized T and B cells pass through the mesenteric lymph nodes and enter the blood stream via the thoracic duct lymph. From the blood stream, these cells settle in the lamina propria of the gut, upper respiratory tract and glandular tissues (mammary, lacrimal, salivary, etc)
- Studies suggest that salivary IgA responses can be induced by oral administration of *S. mutans* antigens of various forms, and that the antibody-mediated protection may result from inhibition of GTF activity or from reaction with cell surface receptors important in adherence.

Stimulation of serum antibodies

- Animals are repeatedly injected using killed cariogenic bacteria
- Thus, these animals develop high serum levels of specific antibodies (IgG) to these bacteria
- However, the effect on caries was not found to be uniform
- Intraoral submucosal injection is apparently more effective than intravenous, based on experiments on monkeys done

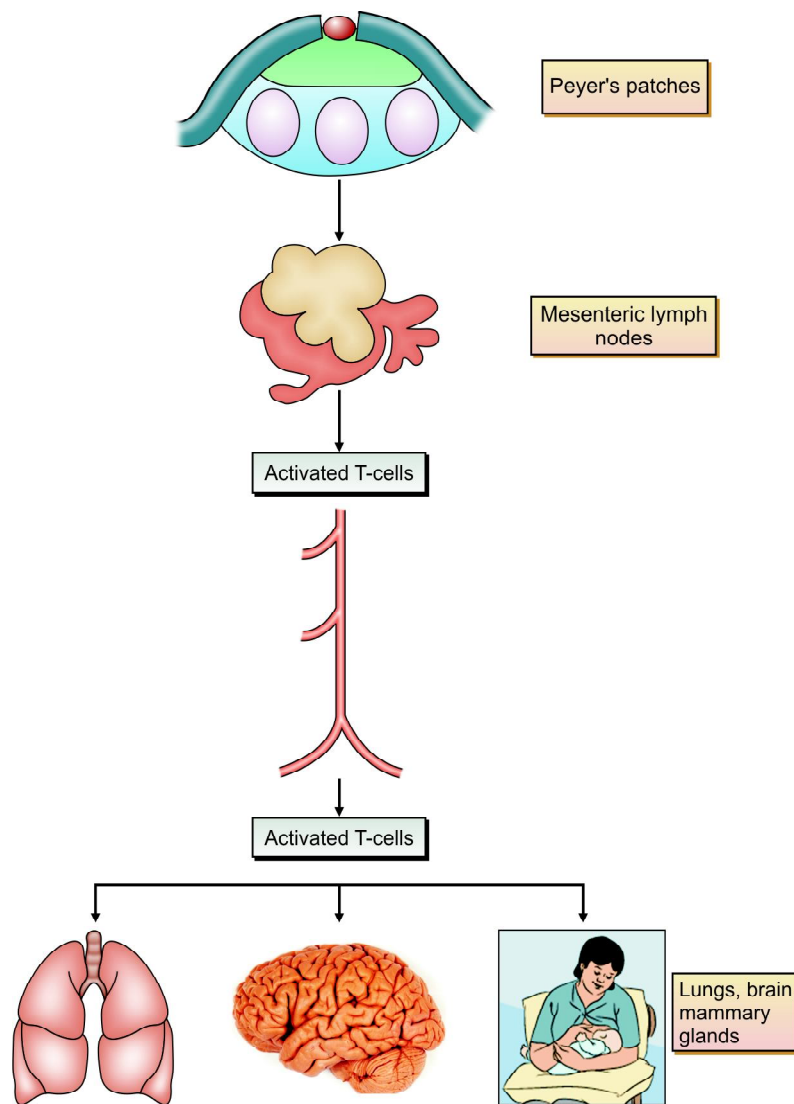


FIGURE 2.8: Schematic representation of pathway for induction of sIgA responses in distant mucosal tissues

with intravenously and submucosally administered avirulent strains of *S. mutans* and GTF

- **McGhee and Michalek, 1981**, stated that since sIgA is the principal immunoglobulin in external secretions, including saliva, local induction of antibodies of these types should be of greater importance in caries immunity.¹⁵

Human Studies

Secretory IgA

- Volunteers swallowed capsules containing formalin killed *S. mutans* daily for several weeks.
- Salivary and lacrimal IgA antibodies were detected within one week; however no change in serum antibody titers was noted

- Oral administration of GTF from *S. sobrinus* raised the level of anti-GTF salivary IgA and interfered with repopulation of the oral cavity by *S. mutans*; however, these effects were short lived.

Serum antibodies

- Presence and titer of serum antibodies to *S. mutans* and *S. sanguis* increases with age from early infancy to around 16 years of age
- It is not a very successful mode of immunization because *S. mutans* possesses antigenic components that elicit antibodies that cross react with human heart muscle (sarcolemmal sheaths)
- Any vaccine that may induce myocarditis represents an unacceptable risk with no justifiable gain

Passive Immunity

- Studies on rats have shown that the offspring of vaccinated rats were protected from colonization by *S. mutans* by the passive transfer of antibody via the colostrum and milk
- In humans, infection by *S. mutans* does not occur till the deciduous teeth erupt, and by that time, most of the infants are no longer nursing
- Hence, tests were done where weanling rats were fed milk either from cows that had been previously immunized with *S. mutans* vaccine or from nonimmunized cows. When the rats were subsequently challenged with an infecting dose of *S. mutans*, those rats which had passively received the antibody in cow's milk were protected against the infection.

Outlook Towards Caries Immunization

- The agglutinating activity of standardized sIgA against strains of oral streptococci changes over time because of detectable alterations in bacterial antigens
- Serum antibodies may be an effective approach to vaccination, but the application of the vaccine requires elimination of possible antibody cross reactions with human heart muscle.

Modern Techniques of Genetic Bioengineering

- Gene from *S. mutans* (GTF) is inserted in DNA of *E. coli* and specific proteins are synthesized. Thus, antibodies against *S. mutans* are produced which can be administered to humans.
- Spleen cells of mice are immunized with cell wall antigen to myeloma cells thereby generating a murine hybridoma cell line, which secretes antibodies against cell wall antigens. These antibodies are purified and subjected to affinity chromatography. Culture fluid of *S. mutans* is passed through the column and only the specific antigen is absorbed. Thus, protein antigens that are suitable as a vaccine but do not elicit antibodies cross reacting with cardiac tissue can be prepared in unlimited quantities.
- While a vaccine against caries is not imminent, the future partial prevention of caries by this means has been predicted.

HOST FACTORS: TOOTH

Tooth Morphology and Arch Form

- Pit and fissure areas of posterior teeth are highly susceptible to caries as food debris and microorganisms readily impact in the fissures.
- Certain surfaces of tooth are more prone to decay whereas **others are not**, e.g. in mandibular first molar, likelihood

of decay in descending order is occlusal, buccal, mesial, distal and lingual.

- There is a variation in susceptibility to caries between different tooth types. Most susceptible permanent teeth are the mandibular first molars then maxillary first molars, then mandibular and maxillary second molars.
- Irregularities in arch form, crowding and overlapping of the teeth also favor the development of carious lesions.

Tooth Composition

- Enamel surface is more caries resistant than the subsurface, as it is continuously being regenerated by precipitation of solid phases like dicalcium phosphate dihydrate and fluorapatite.
- Surface enamel has more minerals and more organic matter but relatively less water.
- Small microdefects at the enamel surface reaching the deeper enamel layer are also seen, which may contribute to the development of caries.

PLAQUE (MICROFLORA)

- Dental plaque is a tenacious microbial deposit which forms on the hard tissue surfaces of mouth, comprising living, dead and dying bacteria and their products, together with the host compounds derived from saliva
- Plaque contains the microorganisms involved in initiation and propagation of caries
- Plaque is generally found in anatomical areas protected from host defenses, e.g. occlusal fissures, interproximal areas, etc. (Fig. 2.9)
- Specific and nonspecific plaque hypothesis:
 - Although *streptococcus mutans* is recognized as the major organism for formation of caries, there is still controversy whether a specific group of organisms are responsible for formation of caries, i.e. the specific plaque hypothesis or disease is caused by a heterogeneous mixture of nonspecific bacteria, i.e. the nonspecific plaque hypothesis.

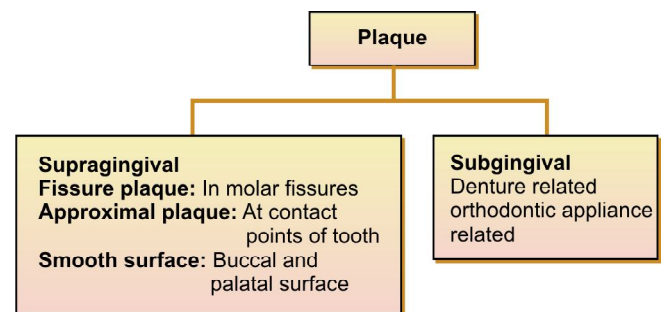


FIGURE 2.9: Schematic representation of type of plaques and areas in which they occur

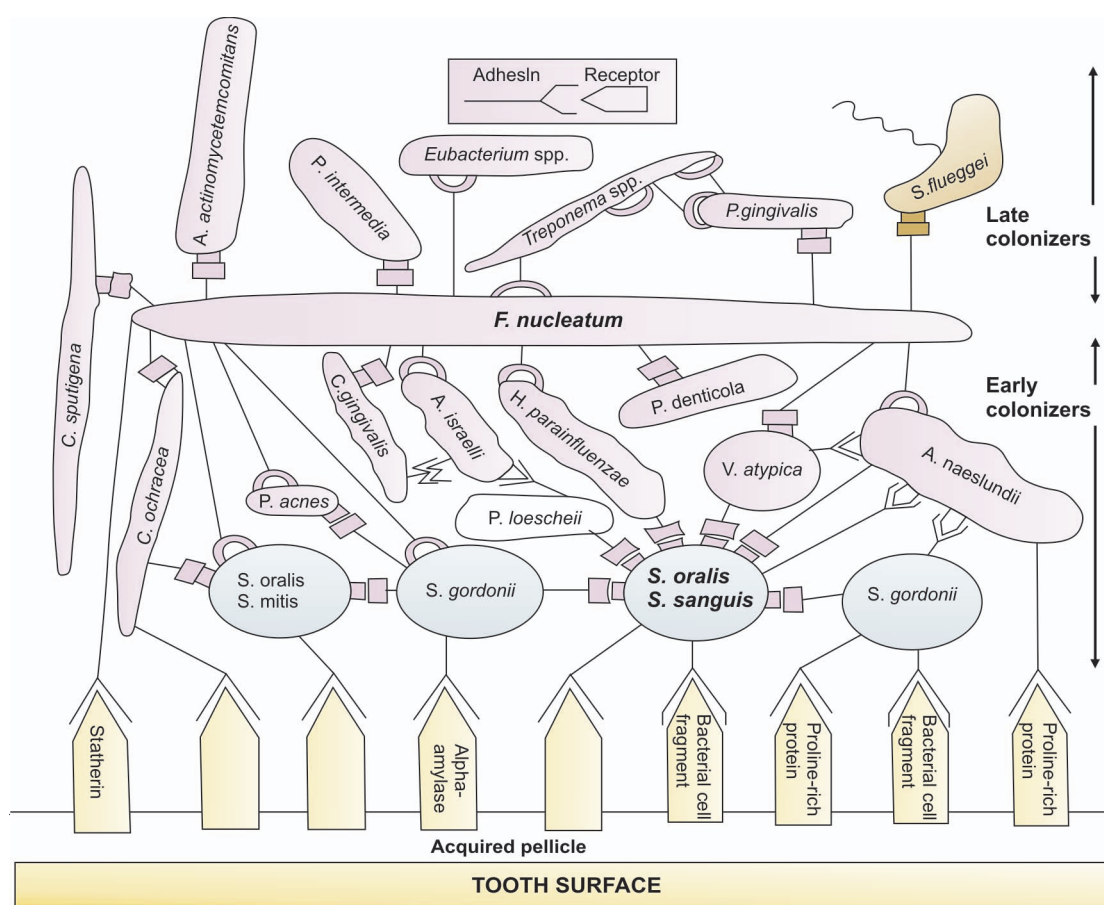


FIGURE 2.10: Intermolecular interactions involved in plaque formation

- There is a lot of controversy about the specific plaque hypothesis because some authors say that *streptococcus mutans* may not be found at the same site in the same mouth at different times and also although *streptococcus mutans* is responsible for formation of caries, there are some nonspecific microorganisms having potential for formation of caries.
- Microbial colonization in plaque occurs in the following manner (Fig. 2.10):
 - Initially, microorganisms attach to the tooth surface by van der Waal's forces. Firm attachment is achieved by a specific mechanism between molecules of microbial cells and pellicle
 - **Initial colonizers** are *S. sanguis*, *S. oralis* and *S. mitis* alongwith Actinomyces and gram negative bacteria, e.g. *Hemophilus* and *Neisseria*
 - Attachment by recognition system on bacterial surface enables components of bacterial surface adhesions to bind to the complementary molecules in the pellicle
 - Microbial enzymatic activity results in destruction of receptors for some species and also creates new hidden receptors (cryptitopes) for the other species. This is an important factor in regulation of colonization (**Gibbons et al 1989**)¹⁶
- *S. mutans* is less efficient than *S. sanguis* in adhering to the tooth surface.
- Microbial succession:
 - As microbiota ages there is a shift from streptococcus dominated plaque to plaque dominated by actinomyces (**Loesche and Syed, 1978**).¹⁷ Such population shifts are known as **microbial succession**
- Pioneer bacteria:
 - The first bacteria to be established in plaque are the **pioneer bacteria**
- Climax community:
 - The plaque environment is attractive to secondary invaders or unfavorable for the preceding microbial colonies because of the lack of nutrients. Decrease in oxygen results in shift of flora from aerobes to obligate anaerobes. The dying bacteria are constantly replaced by new ones. As a result of this dynamic process, the plaque mass reaches a critical size at which a balance

between the deposition and loss of plaque bacteria is established; this community is termed as the *climax community*

- Microbiology of mature smooth surface/approximal plaque:
 - Prominent microflora belong to genus actinomyces especially *A. naeslundii* (**Bowen et al 1975**).¹⁸ Mean percentage of streptococci is lower. Veillonella species are found in high numbers.

Dental Plaque and Caries

- *Streptococcus mutans* is considered to be the main culprit behind causing smooth surface caries
- In a cross-sectional study, 71 percent of fissure caries had viable counts of *S. mutans*, i.e. greater than 10 percent of total cultivable plaque microflora whereas 70 percent of caries free fissures had no detectable *S. mutans* (**Loesche et al 1975**)¹⁹
- In a longitudinal study of fissures, proportions of *S. mutans* increased significantly at the time of diagnosis of the lesion or when a patient was prompted to visit a dentist because of symptoms in the tooth (**Loesche and Straffon 1979**)²⁰
- In a study on Dutch army recruits aged 18 to 20 years where *S. mutans* were subdivided, it was found that *S. mutans* serotype c was isolated from caries active as well as caries free individuals while *S. sobrinus* was isolated from caries active recruits
- A longitudinal study on patients undergoing radiation treatment and showing rampant caries showed that there was increased number of lactobacillus and *S. mutans* in saliva and plaque
- Similar organisms were found in early childhood caries (nursing bottle caries) suffered by young infants.

Microbiology of Root Surface Caries

- Early studies have indicated the role of actinomyces.
- **Billings et al, 1985**,²¹ **Brown et al, 1986**,²² suggested that *S. mutans* alone or in combination with lactobacilli were found in higher numbers in root surface carious lesions.
- Studies have shown that microflora of root surface caries, in addition to *S. mutans* and lactobacilli, commonly includes species belonging to actinomyces, non-mutans streptococci, bifidobacterium, rothia, veillonella, candida, enterococci and other gram negative species (**Bowden, 1990**,²³ **Nyvad and Kilian, 1987**).²⁴
- In advanced lesions, significantly high levels of *S. mutans* were reported at the expense of actinomyces while lactobacilli were common from sites of soft and necrotic dentin (**Shupbach et al, 1996**).²⁵
- Other studies have reported a high proportion of lactobacilli and gram positive rods from infected dentin like *A. israeli* and *A. gerencseriae*.

- Anaerobic Eubacterium Saburreum also formed a considerable proportion of bacteria in advanced cavitated dentinal lesions.

Pathogenic Properties of Cariogenic Bacteria

- Ability to transport fermentable sugars rapidly when in competition with other plaque bacteria and conversion of sugars to acid
- Presence of intracellular and extracellular polysaccharides. Extracellular polysaccharides include glucans and fructans both of which contribute to plaque matrix. Intracellular polysaccharides are glycogen like storage compounds that can be used for energy production and can be converted to acid when free sugars are not available
- Ability to maintain sugar metabolism under extreme environmental conditions at low pH. *S. mutans* and lactobacilli are acidogenic. This is because of:
 - Ability to maintain free intracellular environment and pump out protons even under acidic conditions.
 - Possession of enzymes with more acidic pH optimum.
 - Production of specific acid-stress response proteins.

MICROFLORA RESPONSIBLE FOR CARIES

- **Gram positive cocci:** Streptococci
 - *S. sanguis*
 - *S. mitior*
 - *S. mutans*
 - *S. salivarius*
 - *S. milleri*
- **Gram negative cocci:**
 - *Neisseria* and *Branhamella*
 - *Veillonella*
- **Gram positive rods and filaments:**
 - *Lactobacillus*
 - *Actinomyces*
 - *Arachnia*
 - *Eubacterium*
 - *Propionibacterium*
 - *Bacterionema*
 - *Rothia*
 - *Bifidobacterium*
- **Gram negative rods and filaments:**
 - *Bacteroides*
 - *Fusobacterium*
 - *Capnocytophaga*
 - *Selenomonas*

Streptococcus

Streptococcus is a genus of spherical Gram-positive bacteria belonging to the phylum Firmicutes and the lactic acid bacteria



FIGURE 2.11: Streptococci occurring in chains

group. Cellular division occurs along a single axis in these bacteria, and thus they grow in chains or pairs, hence the name from Greek *streptos*, meaning easily bent or twisted, like a chain (twisted chain) (Fig. 2.11).

Role of streptococcus mutans:

- It comes under the category of α -hemolytic streptococci.
- Evidence of the role of streptococcus mutans in dental caries includes the following:
 - Correlations of mutans streptococci in saliva and plaque with the prevalence and incidence of caries. (Mattee MIN et al, 1992;²⁶ Krishnakumar R et al, 2002;²⁷ Barsamian-Wunsch P et al, 2004;²⁸ Ersin et al, 2006)²⁹
 - It can be isolated from the tooth surface immediately before development of caries
 - Positive correlation has been found between the progression of carious lesions and *S. mutans* count
 - *S. mutans* has the property of production of extracellular polysaccharides from sucrose (which help to cement the plaque organisms together and to the tooth surface)
 - It has the ability to initiate and maintain microbial growth and to continue acid production at low pH values
 - It can rapidly metabolize sugars to lactic acid and other organic acids
 - Ability to attain critical pH for enamel demineralization more rapidly than other common plaque bacteria
 - Ability to produce intracellular polysaccharides as glycogen which may act as a food store for use when dietary carbohydrates are low.
- Other cariogenic streptococci species responsible for induction of caries:

- *S. salivarius*: Present in saliva, epithelial surfaces of tongue, throat and establishes itself in dental plaque
- *S. sanguis*: Present in dental plaque and is capable of producing adhesive extracellular polymers which aid in colonization of cariogenic organisms
- *S. mitior*: Commonly isolated from plaque, present in smooth surface and pit and fissure caries along with other strains
- *S. milleri*: Also present in dental plaque and produces enzymes which help in sucrose degradation.
- Other streptococcal strains involved are *S. oralis*, *S. lactis*, *S. fecalis* and *S. bovis*.

Lactobacillus (Fig. 2.12)

It is a gram positive bacillus, facultative anaerobe and found in a small percentage in normal flora. Mostly *lactobacillus acidophilus* and *lactobacillus casei* are mainly responsible for smooth surface caries.

Role of lactobacilli:

They are considered to be candidate organisms in caries because:

- Their high numbers in most carious lesions affecting enamel have been reported
- The positive correlation between their numbers in plaque and saliva and caries activity has been established
- Their ability to grow in low pH environments below pH 5 and to produce lactic acid has been established
- Their ability to synthesize both extracellular and intracellular polysaccharides from sucrose also aids in the production of caries
- They have two major properties necessary for progression of a carious lesion:
 - Acidogenic: produce acids and cause demineralization of enamel surface
 - Aciduric: particularly grow well in acid environment.

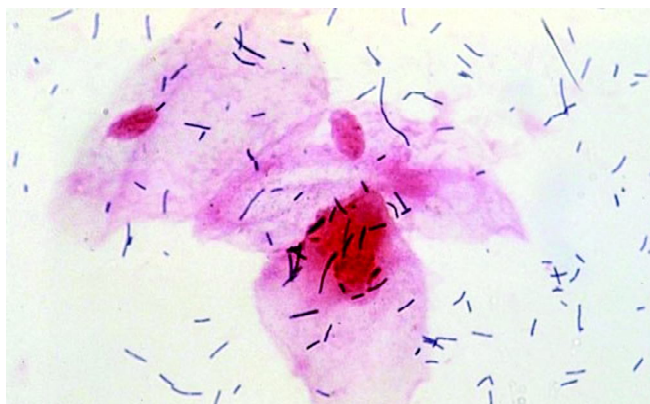


FIGURE 2.12: Lactobacilli occurring as rods

Although the role of lactobacilli in caries is not as well defined as streptococci, it is believed by most investigators that:

- They are involved more in the progression of deep enamel lesions
- They are pioneer organisms in the advancing front of the carious process especially in dentin.

Actinomyces

Actinomyces is a genus of the actinobacteria class of bacteria. They are all Gram-positive and can be either anaerobic or facultatively anaerobic. *Actinomyces* species do not form endospores and while individual bacteria are rod-shaped morphologically, *Actinomyces* colonies form fungus-like branched networks of hyphae.

- *Actinomyces naeslundii* and *actinomyces viscosus* are mostly found in dental plaque
- Trauma, foreign bodies or poor oral hygiene may favor tissue invasion by actinomyces
- In human beings, they occur in four clinical forms:
 - *Cervicofacial*: with indurated lesion on cheek and submaxillary region. Caused mainly due to dental infection.
 - *Thoracic*: with lesions in lung that may spread outwards through the chest wall.
 - *Abdominal*: where lesions are found around cecum with involvement of neighboring tissues and abdominal wall.
 - *Pelvic*
- It has been incriminated in inflammatory diseases of the oral cavity such as gingivitis and periodontitis and is also found in subgingival plaque leading to root surface caries.

Diagnosis is made by presence of sulfur granules which are white or yellowish and range in size from minute specs to about 5 mm. They are examined microscopically under a cover slip (Fig. 2.13).

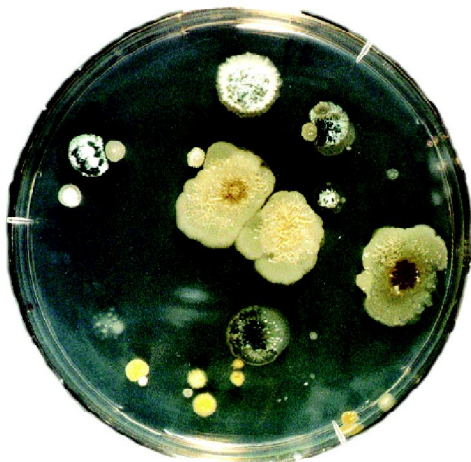


FIGURE 2.13: *Actinomyces* showing yellow sulfur granules

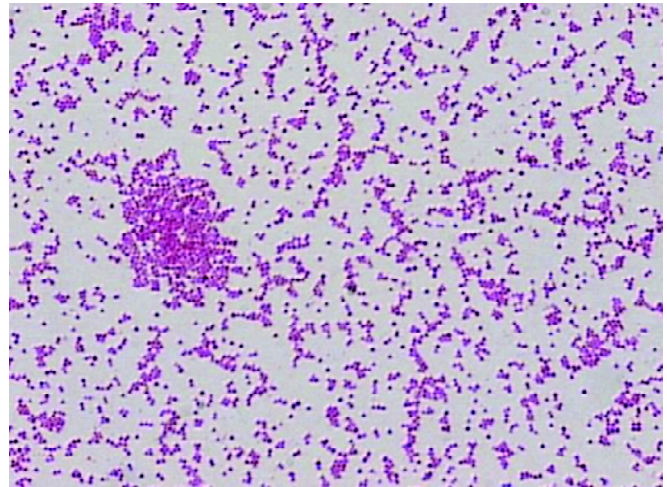


FIGURE 2.14: *Veillonella*

They can be crushed between slides, gram stained and then examined.

Under the microscope, gram positive filaments are observed surrounded by radiating club shaped structures.

Role of actinomyces:

- These are associated with development of root surface caries, in that the calcified tissues are softened without obvious cavitation.
- Some studies have reported both mutans streptococci and lactobacilli in these lesions.

Veillonella (Fig. 2.14)

- It is a coccus, an obligate anaerobe, isolated from most surfaces in oral cavity
- High numbers are found on tongue and also in most of the supragingival plaque.

Role of veillonella:

- It is present in more numbers in supragingival plaque samples
- They require lactate for their growth but are unable to metabolize normal dietary carbohydrates; they therefore utilize lactate and other intermediate metabolites formed by plaque bacteria as energy sources and convert it into a range of other less cariogenic organic acids, e.g. propionic acid
- Hence, these organisms may have a beneficial effect on dental caries.

DIETARY FACTORS

- Dental caries is widely accepted as being caused by the ingestion of fermentable carbohydrates particularly sucrose.

- Fermentable carbohydrates are generally eaten as components of food that contain other ingredients and have different textures.
- The cariogenic potential of food depends upon:
 - Its ability to be retained by teeth
 - Its ability to form acids
 - Its ability to dissolve enamel
 - Its ability to neutralize buffer acids
- The frequency and time of ingestion of food are also important
- Sucrose containing food becomes more cariogenic if it is eaten frequently
- Food eaten at meals produces less caries than eating the same food between meals.

Important Studies Relating Diet with Dental Caries

Vipeholm study, 1954, was a five year investigation of 436 adult inmates at a mental institution at the Vipeholm hospital, Sweden.³⁰

- According to the experimental design, the inmates were divided into seven groups with varying sugar intake:
 - A control group
 - A sucrose group (300 gm of sucrose given in solution but reduced to 75 gm during the last two years)
 - A bread group (345 gm of sweet bread containing 50 gm of sugar daily)
 - A chocolate group (65 gm of milk chocolate daily between meals during the last two years).
 - A caramel group (22 caramels [70 gm of sugar] in four portions between meals)
 - An eight-toffee group (eight sticky toffees [60 gm of sugar] daily for three years)
 - A 24-toffee group (24 sticky toffees [120 gm of sugar] for 18 months)
- This study gave the following conclusions:
 - An increase in carbohydrate (mostly sugar) definitely increases the caries activity.
 - The risk of caries is greater if the sugar is consumed in a form that will be retained on the surfaces of teeth
 - The risk of sugar increasing caries activity is greatest if the sugar is consumed between meals and in a form that tends to be retained on the surfaces of the teeth
 - The increase in caries activity varies widely between individuals
 - Upon withdrawal of the sugar-rich foods, the increased caries activity rapidly disappears
 - Caries lesions may continue to appear despite the avoidance of refined sugar and maximum restrictions of natural sugars and dietary carbohydrate
 - A high concentration of sugar in solution and its prolonged retention on tooth surfaces leads to increased caries activity
 - The clearance time of the sugar correlates closely with caries activity.

Hopewood house study, 1958, was a longitudinal study of ten years on 3 to 14 year children residing at Hopewood house, Bowral, New South Wales.³¹

- These institutionalized children were genetically heterogeneous
- They were on a strict lactovegetarian diet with absence of meat and restriction of refined carbohydrate, except for weekends. Between-meal snacks were limited to milk, fruit and raw vegetables
- Caries prevalence was almost negligible in the primary dentition in these children and approximately one tenth that seen in the permanent teeth of the average Australian child
- Surprisingly, their oral hygiene was extremely poor (75% were found to have gingivitis)
- As these children grew older and left Hopewood House, a sharp rise in caries rate occurred at about the age range 13 to 18 years
- This increase shows the deleterious effects to dental health caused by a strongly cariogenic diet and also the fact that the caries-free teeth did not acquire any permanent immunity to caries.

Seventh day adventist children, 1958, complied to principles depending on religious motivation advocated by the Seventh Day Adventist dietary counsels.³²

- This included abstinence from certain animal proteins, and limited use of sugar, sticky desserts, highly refined starches and between meal snacking
- They showed a lower caries prevalence than the non-adventist children in the same geographic location and socioeconomic stratum.

Turku sugar studies, 1975, were carried out in Turku, Finland by Scheinin, Makinen et al to test the effects of chronic consumption of sucrose, fructose and xylitol on dental and general health.³³

- In the two year feeding study, 125 young adults divided into three experimental groups: sucrose group (N = 35), fructose group (N = 38), xylitol group (N = 52), consumed the entire dietary intake using these sugars exclusively
- They were investigated by a comprehensive program including clinical, radiographic, biochemical and microbiological determinants of health
- Conclusions were:
 - Sucrose chewing gum was found to be definitely cariogenic
 - Between meals chewing of xylitol gum produced an anticariogenic effect
 - Fructose was as cariogenic as sucrose for the first year, but showed lower rates in the second year
 - Xylitol consumption resulted in a reduction in dental caries.

TIME

- Time factor is certainly not the least important of the factors involved in the production of caries
- Development of caries is a slow process that may extend for months before the development of a perceptible cavitation but when the challenge is overwhelming, lesions may start to form within three weeks
- Hence, the time duration for which the tooth is subjected to cariogenic food substrates is extremely important in regulating the phases of demineralization and remineralization.

CLASSIFICATION OF DENTAL CARIES

- Based on tooth morphology:
 - Pit and fissure caries
 - Smooth surface caries
 - Root cementum caries
 - Linear enamel caries
- GV Black's classification³⁴ (Fig. 2.15):
 - Class I: Caries involving occlusal surfaces of posterior teeth, caries involving occlusal 2/3rd of buccal and lingual surfaces of posterior teeth, caries involving the lingual pits of maxillary incisors.
 - Class II: Caries involving proximal surfaces of posterior teeth.
 - Class III: Caries involving proximal surfaces of anterior teeth, not involving the incisal angle.
 - Class IV: Proximal caries involving incisal angle of anterior teeth.
 - Class V: Caries involving labial or buccal enamel near the dentino-enamel or cemento-enamel junction.
 - Class VI: Caries involving cusp tips of posterior teeth and incisal edges of anterior teeth.
- Based on severity and rate of caries progression:
 - Rampant caries
 - Acute caries
 - Chronic caries
- Related to degree and rate of progression of caries:
 - Incipient caries
 - Arrested caries
 - Recurrent caries
- Classification based on chronology:
 - Nursing bottle caries
 - Adolescent caries
- Classification based on location:
 - Primary caries
 - Backward caries
 - Forward caries
 - Residual caries
 - Root surface caries
 - Secondary caries
- Classification based on extent of caries:
 - Incipient (reversible)
 - Cavitated (irreversible)
- A recent classification based on site and size proposed by Graham J. Mount and Hume, 1997³⁵ (Table 2.3).
- Site:
 - Site 1: All lesions originating in pits and fissure
 - Site 2: All lesions associated with contact areas
 - Site 3: Lesions originating close to gingival margin
- Size:
 - Size 1: Lesion that has progressed to the point where it is first beyond remineralization
 - Size 2: Larger lesions, but there is still sufficient sound tooth structure remaining to support the restoration without further modification of the cavity beyond caries removal
 - Size 3: More extensive lesion that leaves remaining tooth structure at a risk of further bulk failure
 - Size 4: Extensive lesion in which there has already been serious loss of tooth structure.

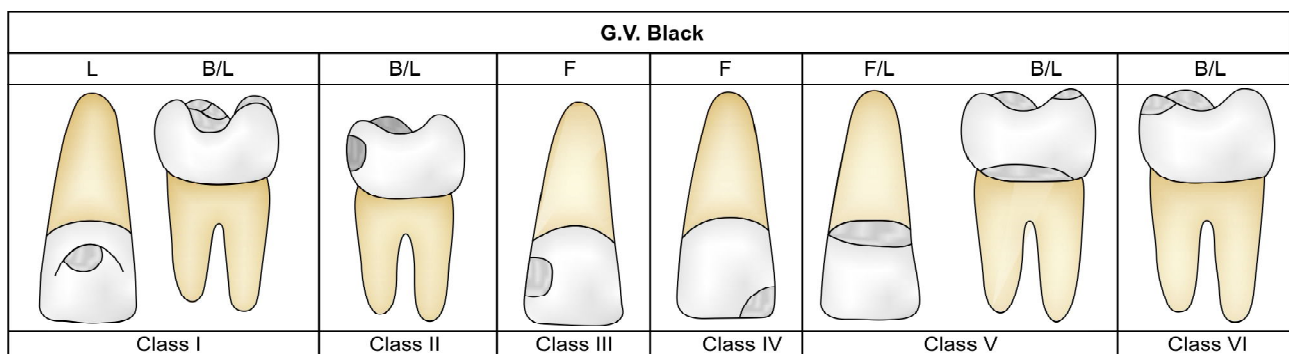
**FIGURE 2.15:** GV Black's classification of dental caries

TABLE 2.3: Classification of caries:Graham J. Mount and Hume, 1997

Sr. No.	Site	Size			
		1 = minimal	2 = moderate	3 = enlarged	4 = extensive
1.	Pits and fissures	1.1	1.2	1.3	1.4
2.	Proximal surfaces	2.1	2.2	2.3	2.4
3.	Cervical areas	3.1	3.2	3.3	3.4

HISTOPATHOLOGY OF DENTAL CARIES

- Familiarity with the shape of the lesion in different locations is of fundamental importance in understanding the design of cavity preparations.
- Caries is commonly considered a chronic disease in man because lesions develop over a period of months or years.
- The average time from the stage of incipient caries to clinical caries is 18 ± 6 months.
- In some patients with xerostomia, following radiation therapy, caries can be detected clinically within 3 months.

CARIES OF ENAMEL

Macroscopic Changes in Enamel

On smooth surfaces: Loss of transparency is seen resulting in opaque chalky region (white spot); this indicates subsurface demineralization, where the critical pH of the subsurface hydroxyapatite is reached and there demineralization begins; however, there is no break in the surface of enamel yet.

- In lesions where caries has progressed more slowly or become arrested, brown or yellow pigmentation of enamel may be seen.
- When sectioned longitudinally, cavitated carious lesions are cone shaped with the apex directed towards dentin.
- What determines the shape of the lesion is still not definitely proved, but many investigators suggest that the carious lesion follows the direction of the enamel rods and hypocalcified structures of enamel.

On occlusal surfaces: There are deep invaginations called fissures. They can be classified as (Fig. 2.16):

- V type: Wide at top and gradually narrowing towards the bottom (34%)
- U type: Almost same width from top to bottom (14%)
- I type: An extremely narrow slit (19%)
- IK type: Extremely narrow slit associated with larger space at the bottom (26%)
- Other types (7%)
- On the occlusal surface, a carious lesion starts at both sides of the fissure wall rather than at the base, penetrating nearly perpendicularly towards the dentinoenamel junction
- Visual changes are chalkiness or yellow, brown or black discoloration (Figs 2.17 and 2.18)

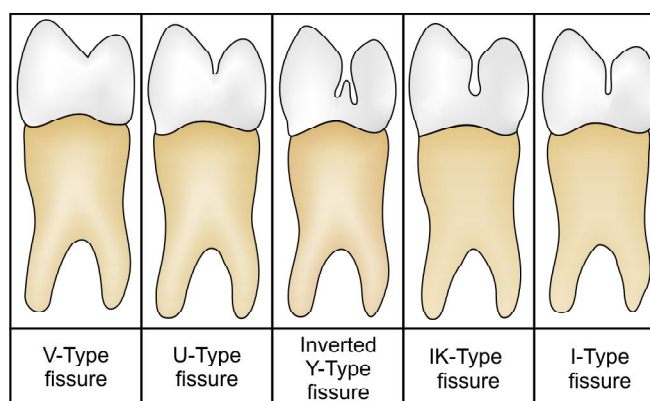


FIGURE 2.16: Schematic representation of various types of fissures on teeth



FIGURE 2.17: Incipient caries showing chalky white appearance on the tooth surface

- In newly erupted teeth, a brown stain is indicative of underlying decay, while in teeth of older individuals, it may be due to arrested or remineralized lesions
- Lesions are cone shaped with base directed towards dentin and apex towards the enamel.



FIGURE 2.18: Caries in deciduous teeth

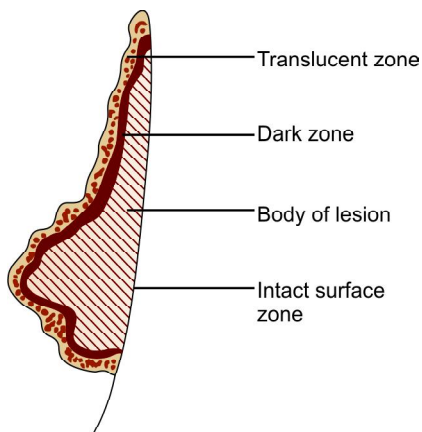


FIGURE 2.19: Four histopathological zones of caries

Microscopic Changes in Enamel

- In early stages, caries causes minimal damage to the outer smooth surface but considerable demineralization occurs below the surface.
- Histopathologically, 3-7 zones can be seen of which 4 zones are clearly distinguishable.
- Starting from inner advancing front of the lesion (from bottom to top) (Fig. 2.19)
 - Translucent zone
 - Dark zone
 - Body of the lesion
 - Surface layer

Translucent zone

- Only seen when longitudinal ground sections are examined.
- Formation of this zone appears to be the earliest change in the advancing front of the lesion
- Appears structureless and characterized by approximately 1.2 percent loss of mineral
- Shows negative birefringence in polarized light
- Lesion appears radiopaque on radiographs
- Pore volume is one percent (intact enamel pore volume is 0.1%).

Dark zone

- Common feature of a carious lesion
- Shows positive birefringence in polarized light (normal enamel has negative birefringence)
- Mineral loss is six percent
- Appears radiopaque on radiographs
- Pore volume two to four percent.

Body of lesion

- Largest zone
- Shows positive birefringence
- Mineral loss is 24 percent
- Corresponding increase in unbound water and organic content due to ingress of bacteria and saliva
- Appears radiolucent on radiographs
- Pore volume 5 to 25 percent.

Surface layer

- Ranges between 20 and 100 μm thickness
- Appears unaffected in initial lesion as compared with subsurface zones
- Negative birefringence in polarized light
- Radiopaque on radiographs
- Mineral loss 10 percent
- Pore volume <1 percent

Ultrastructural Changes in Enamel (Fig. 2.20)

- Scattered destruction of individual apatite crystals
- Dissolution results in broadening of intercrystalline space, which becomes filled with amorphous material, some of which gives a positive histochemical reaction of carbohydrates
- More advanced dissolution has been seen of the crystals that are directed vertically into the demineralizing zone in the center of heads of the prisms. There is a lesser degree of damage to the crystals in the tails of the prisms that are distributed at an angle or lengthwise to the demineralizing zone
- Dissolution starts in the center of one end of the crystal and proceeds anisotropically along the C-axis. The central

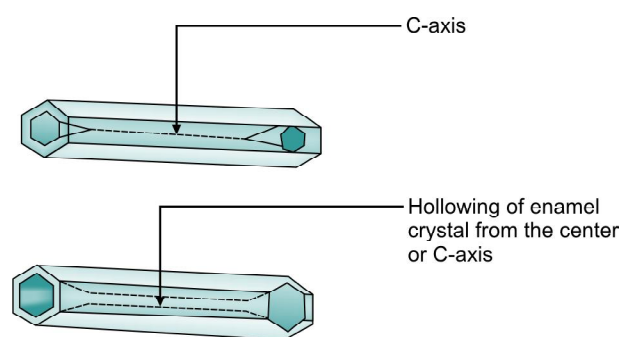


FIGURE 2.20: Ultrastructure of enamel caries spreading along C-axis anisotropically

hole thus formed extends along the entire crystal length. The central dissolution parallels the lateral external crystal surface, resulting in hollow hexagons or rectangles. After formation of the central hole, the dissolution extends as lateral localized destruction towards the external surface.

- Bacterial colonies observed by scanning electron microscope consist primarily of rod shaped and occasionally filamentous micro-organisms.

CARIES OF DENTIN

Macroscopic Changes in Dentin

- On reaching dentin, the carious lesion spreads laterally along the dentinoenamel junction such that a cone shaped lesion is formed, where the base of the lesion lies towards the DEJ and the apex points towards the pulp.
- The lesion proceeds along a saucer-shaped front and follows the direction of the dentinal tubules.
- Affected dentin displays different degrees of discoloration ranging from brown to dark brown to almost black.

Microscopic Changes in Dentin

- Pathological changes have been divided into five zones from pulpwards to carious lesion (Fig. 2.21):
 1. Zone of fatty degeneration
 2. Zone of dentinal sclerosis
 3. Zone of demineralization
 4. Zone of bacterial invasion
 5. Zone of decomposed dentin

Zone of fatty degeneration

- After specific staining, lipid has been seen in active lesions.
- Two types of lipid staining have been seen:
 1. One that is superficial due to bacterial origin
 2. Other is due to unmasking of lipids present in peritubular dentin

Zone of dentinal sclerosis

- Altered tubules acquire a refractive index similar to the adjacent matrix presenting a homogeneous transparent appearance in transmitted light. That is the translucent zone of dentin identical to the sclerosed dentin.
- This dentin is impermeable to stains like methylene blue.
- It represents an attempt to block the advancing carious lesion.

Zone of demineralization

- Next to sclerosed dentin, it is a narrow zone.
- Affects the intertubular matrix.
- Occlusion of tubules observed in this zone is due to reprecipitation of crystalline material that had dissolved during the carious process.

Zone of bacterial decomposition

- Most noticeable change observed in carious dentin.
- Lumen of tubule is distended giving a ballooned or dilated appearance.
- These dilated appearances are referred to as “Liquefaction foci of Miller”.
- Misnomer because distentions are filled with bacteria and debris and not liquid.

Zone of decomposed dentin

- These dilatations eventually coalesce forming the outermost zone of decomposed dentin.
- Cracks or clefts containing bacteria and necrotic tissue appear at right angles to the course of dentin tubules.
- This zone may follow the course of incremental lines or arise by coalescence of liquefaction foci or by extension of proteolytic activity along interconnecting lateral branches of odontoblast tubules.

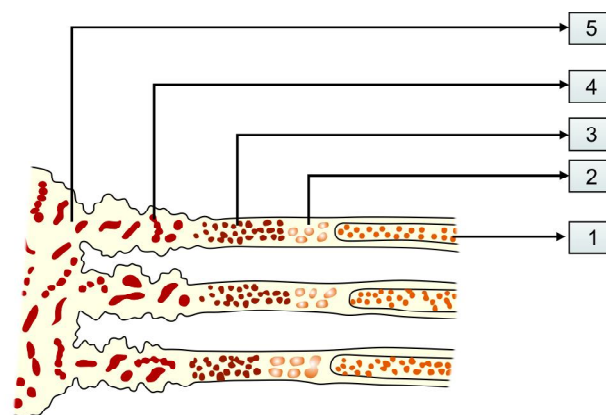


FIGURE 2.21: Histopathologic picture of dentinal caries showing various zones

STAINS TO DETECT CARIES

- *Enamel lesions:* Permeable to methyl green and contain free calcium ions detected by Alizarin red S.
- Normal enamel remains uncolored by these dyes.
- *Dentinal lesions:* Decomposed and bacterial zones stain red with basic fuchsin.
- Acid red dyes react with collagen that has been treated with lactic acid but not with intact dentinal collagens.

EARLY CHILDHOOD CARIES

Way back in 1962, Dr. Elias Fass published the first comprehensive description of caries in infants. He can be quoted as: *“Nothing is as shocking to a dentist as the examination of a child patient suffering from rampant caries.”* The foundations established by this paper have essentially remained unchanged over the past 45 years. *Early childhood caries* (ECC) is the new term for an infectious disease that affects the teeth of infants and toddlers. Its prevalence rate in developing countries has been shown to be as high as 70 percent. The cost of treating ECC is very high and unfortunately, the risk factors for ECC point to various parenting practices such as the use of baby bottles containing sweetened beverages.³⁶

During the first year of life, the infant undergoes a rapid development that is accompanied by drastic changes within the oral environment. Some of these changes may be related to the emergence of the first teeth during this time period. The presence of teeth facilitates a shift in nutrition from fluid to solid food, and concomitantly, the oral microbial community changes, because the teeth provide new ecological niches for bacterial colonization.³⁷

Children suffer from many infectious diseases during the first three years of life around the time of eruption of the deciduous teeth. Early childhood caries, which is a combination of a child being infected with cariogenic bacteria and the frequent ingestion of sugar, is one of such diseases. Despite improvement over several decades, oral disease amongst the children remains a serious problem.³⁸

Although the etiology of ECC is similar to other types of coronal and smooth surface caries, the biology may differ in some respects.

The bacterial flora and host defense systems in the young infant are in the process of being established. In addition, the tooth surfaces are newly erupted and immature, and may show hypoplastic defects.

Although dental caries has been declining globally in the general population, more so among older children, caries prevalence in younger ones has not shown a significant decline.³⁸

The caries prevalence in the primary dentition of preschool children in urban Pondicherry, India was found to be 44.4 percent with 26.7 percent in the maxillary arch and 36.9 percent in the mandibular arch;³⁹ the caries prevalence in preschool children in Dharwad city, India, was found to be 54.1 percent,³⁸ a very good indicator of the widespread hold of caries over our society.

ECC is a result of an interaction of the factors involved in other types of dental caries, viz cariogenic bacteria, refined carbohydrates, host factors and time. The dietary factors at work in the causation of ECC include frequent consumption of liquids containing fermentable carbohydrates, particularly through a nursing bottle at sleep times. Juices, sodas, infant formula and sweetened beverages have been implicated in ECC. When taken via a nursing bottle while the infant sleeps, these liquids pool around the maxillary incisors and can cause rapidly progressive, severe destruction of tooth structure beginning typically on smooth surfaces around the cervical margins of teeth or labial, lingual and proximal surfaces of primary maxillary incisors, areas otherwise considered to be affected to a minor extent. This indicates a particularly virulent form of caries, which starts soon after teeth erupt, earlier than 12 months to two years of age, and it proceeds rapidly, to involve primary molars and canines.

Fass, 1962, emphasized the possible cariogenic effects of milk fed from a bottle to young children in order to soothe them and encourage sleep. Under these conditions, milk may remain in the mouth and possibly in contact with teeth while saliva flow ceases and swallowing becomes infrequent.⁴⁰

Breast milk is a complete nutritious diet for neonates. However, some children have to settle for infant milk formulae which contain lactose as the main ingredient.⁴¹ These alternate sources of nutrition such as baby bottles containing infant milk formulae or fruit juices are known to be more cariogenic than breast milk. Both soy-based and protein hydrolysate formula contain non-milk extrinsic sugars such as sucrose and glucose syrup as carbohydrate resources. According to European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 1990, the manufacturers were allowed to add other sugars of no more than 20 percent of the total carbohydrate content in follow-on formula.⁴² Breast feeding when continued for a prolonged period of time has also been found to support the development of early childhood caries.

Early childhood caries is a specific form of severe dental caries that affects infants and young children. It is defined as the presence of more than one decayed (non-cavitated or cavitated lesions), missing (due to decay), or filled tooth surface in any primary tooth in a child seventy one months or younger. Severe early childhood caries has been described as in Table 2.4. This presentation of dental caries was formerly

TABLE 2.4: Age and surfaces involved in severe early childhood caries

Sr. No.	ECC	Age	Presence of caries
1.	Severe form	<3 years of age	Smooth surface caries in ≥ 1 tooth
2.	Severe form	3-5 years of age	≥ 1 cavitated, missing, or filled smooth surface in primary maxillary anterior teeth or decayed, missing, or filled surface (dmfs) score of
		Age-3 years	Greater than 4
		Age-4 years	Greater than 5
		Age-5 years	Greater than 6

termed “baby bottle tooth decay” by Mim Kelly et al, 1987,⁴³ “nursing bottle caries” by Tsamtsouris, 1986, “rampant caries”, “primary tooth caries”, “milk bottle syndrome” by Ripa, 1988,⁴⁴ “early childhood caries” by Davies, 1998⁴⁵ and “maternally derived *Streptococcus mutans* disease.” Nursing caries and rampant caries are both considered forms of early childhood caries and the differences between the two have been outlined as in Table 2.5.

Since 1986, the American Academy of Pediatric Dentistry has adopted a position on infant oral health recommending that the first visit occur within six months of eruption of the first primary tooth.⁴⁶

High risk group children with primary teeth decay should be identified and categorized, which in turn is useful to determine needs for restorations and to implement primary preventive procedures in the targeted group.

RECOMMENDATIONS TO PARENTS BY PEDODONTISTS

- Parents should be educated from time to time about the importance of diet in the development of caries (with regards to the type of carbohydrate).
- Parents should be made aware of the fact that bovine milk is lower in sugar than formula milk and is higher in the protective factors, calcium and phosphorus.⁴⁷ Hence, they should be encouraged to provide bovine milk for their children when an alternative or an adjunct to breast milk is sought.
- Parents should be discouraged from the frequent use of bottles for feeding, especially for prolonged periods at night.
- Parents should be educated about the need for commencement of tooth brushing or cleaning the teeth with clean gauze or a clean muslin cloth, as soon as the first teeth erupt.⁴⁸
- Other primary preventive measures that can be applied during this period include water fluoridation or, in its absence, the administration of fluoride supplements and topical applications of fluoride solutions or varnishes soon

TABLE 2.5: Differences between nursing caries and rampant caries

Sr. No.	Nursing caries	Rampant caries
1.	It is a specific form of rampant caries	Defined by Massler as a suddenly appearing, widespread, rapidly burrowing type of caries, resulting in early involvement of the pulp and affecting those teeth usually regarded as immune to ordinary decay
2.	Usually seen in infants and toddlers	Seen at all ages, including adolescence
3.	Maxillary incisors affected first followed by molars. Mandibular incisors characteristically remain unaffected	All surfaces considered immune to decay are involved including mandibular incisors.
4.	Etiology primarily based upon improper feeding practices such as prolonged bottle feeding containing sweetened milk, fruit juices, etc. at will breast feeding, pacifiers dipped in honey or other sweeteners	Rapid appearance and spread of decay is seen Etiology more so based upon the caries tetrad modified by Newbrun.
5.	Management is based upon: Education (oral hygiene and dietary counseling) Prevention by topical fluoride applications Removal and restoration of carious lesions	Management is based upon: Removal of carious lesions and reduction of <i>Streptococcus mutans</i> count (caries risk) Long-term treatment for restoration of the teeth may be required Adequate follow up to keep the caries risk at a low level
6.	Prenatal counseling of pregnant women with regards to diet and oral hygiene	Dental health education amongst all age groups

after the teeth erupt to increase the resistance of enamel to demineralization.

- Parents and caregivers should be trained to recognize the early signs of the condition, using the "lift the lip" technique.
- Ismail, 1998⁴⁹ and Weintraub, 1998⁵⁰ supported the development of a special "Fall-Asleep-Pacifier", as suggested by Suhonen et al, 1994,⁵¹ that includes a slow-releasing lozenge containing sodium fluoride, xylitol and sorbitol. It is recommended specially for children who have any white spot lesions or incipient caries.

As a preventive measure, the dental professionals must thrive hard to make appropriate feeding of infants and children, a national movement supported by all health professionals. The parents and the pedodontist should work as partners in providing oral health care for children with ECC.

CARIES SUSCEPTIBILITY AND CARIES ACTIVITY

An advance in health research has resulted in a major paradigm shift in the diagnosis, treatment and management of dental caries. Hence, identifying the risk groups followed by providing preventive care is the key to primary prevention. It is a cost beneficial method which is holistic and suitable even among the developing countries.

Caries susceptibility and caries activity tests have been developed with a goal of understanding and identifying oral conditions and have been used to predict future caries activity as well as measure the effectiveness of therapy.

DEFINITIONS

- **Caries activity**—Increment of active lesions (new and recurrent lesions) over a stated period of time.
- **Caries susceptibility**—Inherent tendency of the host and target tissue, the tooth, to be afflicted by the carious process.
- **Caries activity tests**—Tests to measure the degree to which the local environment challenge favors the probability of carious lesions.
- **Sensitivity**—The ability of a test to identify correctly which sound teeth will become carious is termed as sensitivity.
- **Specificity**—The ability of a test to predict no change in the status is termed as specificity.

CARIES SUSCEPTIBILITY TESTING

- **Quantity and quality of saliva:** This is initially determined by visual inspection and questioning. The extremely dry mouth may be identifiable by oral examination. Sometimes, the statement that they frequently drink water or other fluids is an indicator of prolonged dryness. Carry out a stimulated salivary flow rate by asking the patient to chew the paraffin

wax or gum or use a drop of citric acid on the tongue. Collect the saliva in a small graduated vial over a two minute period. Stimulated flow rate of less than 0.7 ml/min should be followed by further assessment of other risk factors.

- **Buffering capacity of saliva:** It is possible to measure buffering capacity using commercially available kits. However, salivary buffering capacity is usually proportional to the flow rate, so the latter is generally considered to be a reasonable indicator.

Originally Dreizen test was used followed by the modified Dreizen test. Both of these are titration tests with the endpoint being determined by a dye color change.

In 1980, Frostell introduced the Dentobuff system.⁵² Paraffin is chewed for two mins and 5 ml of saliva is collected. 1 ml of saliva is taken in a vial of Dentobuff and shaken for 10 secs. Then let CO₂ evaporate for 2 mins. The color of the indicator in the vial is matched with the standard chart.

Results (Table 2.6): A simpler modification of the Dentobuff system using a pH indicator strip has been introduced by Ericson and Bratthall, 1989.⁵⁴

- **Viscosity of saliva:** A special Ostwald pipette with a calibrated bore may be used to measure the viscosity of saliva. 5 ml of water is taken in the pipette and allowed to flow under gravity. The time taken for this flow is measured in seconds. This is followed by a 5 ml saliva specimen.

$$\text{Relative viscosity} = \frac{\text{Time required for flow of saliva}}{\text{Time required for flow of water}}$$

Normal value is around 1.5.

CARIES ACTIVITY TESTS

Uses of caries activity tests:

- To identify high risk groups and individuals.
- To determine the need and extent of personalized preventive measures.
- To serve as an index of the success of therapeutic measures.
- To motivate and monitor the effectiveness of education progress relating to dietary and oral hygiene procedures.
- To evaluate the progress of restorative procedures.

TABLE 2.6: Results interpreted in buffer capacity test in saliva

Sr. No.	Final pH	Color	Buffering capacity
1.	3-4	Yellow	Poor
2.	4.5-5	Green	Intermediate
3.	5.5-6.5	Purple	Good

Ideal Requisites of a Caries Activity Test

- Maximum correlation between predicted and actual caries.
- Reliability and validity.
- Simplicity with regard to technical procedures and skills required.
- Rapid results within few hours or days.
- Measurement of mechanisms involved in caries process.
- Inexpensive, noninvasive, easy to evaluate and applicable in clinical settings.

Lactobacillus colony count test

- Introduced by Hadley, 1933.⁵⁵
- This is done using the conventional plate count method.
- **Principle:** Estimates number of lactobacilli in the patients' saliva by counting number of colonies on tomato peptone agar plates.
- **Procedure:**
 - Patient chews paraffin wax vigorously for 1 to 5 mins, moving the paraffin alternately from side to side.
 - Saliva secreted in three min is collected.
 - Saliva is diluted 1:10 with sterile saline.
 - 1:100 dilution is also prepared.
 - Each dilution is inoculated on Rogosa's SL agar plate for 3 to 4 days at 37°C.
 - Number of colonies are counted using a colony counter.

Results

Refer Table 2.7.

Colorimetric Snyder test

- Introduced by Snyder, 1951.⁵⁶
- **Principle:** Measures the ability of salivary microorganisms to form organic acids from a carbohydrate medium containing Bromocresol green as indicator dye.
- **Procedure:**
 - 0.2 ml stimulated saliva collected by chewing paraffin is mixed with 10 ml melted agar containing medium in a test tube.
 - Incubated at 37°C.
 - Amount of acid produced is detected by changes in pH indicator.
 - Rate of color change checked at 24, 48 and 72 hrs of incubation. This indicates the degree of caries activity.

TABLE 2.7: Results interpreted in *Lactobacillus* colony count test

Sr. No.	No. of organisms per cc	Symbolic designation	Degrees of caries activity suggested
1.	0-1000	±	Little or none
2.	1000-5000	+	Slight
3.	5000-10,000	++	Moderate
4.	More than 10,000	+++ or ++++	Marked

Results following color observations in Snyder's test (Table 2.8)

TABLE 2.8: Results interpreted in Colorimetric Snyder test

Color	24 hours	48 hours	72 hours
Yellow	Marked caries susceptibility	Definite caries susceptibility	Limited caries susceptibility
Green	Continue to incubate and observe at 48 hours	Continue to incubate and observe at 72 hours	Caries inactive

Swab test

- Introduced by Grainger et al 1965.⁵⁷
- Principle is same as Snyder test
- **Procedure:**
 - Oral flora sampled by swabbing the buccal surfaces of teeth with cotton applicator. Since no collection of saliva is required, this test may be used in **very young children**.
 - The cotton applicator is incubated in the medium at 37°C.
 - Change in pH following a 48 hour incubation is read on a pH meter or color change is read by the use of a color comparator.

Results:

- pH 4.1 = Marked caries activity
- pH 4.2-4.4 = Active
- pH 4.5-4.6 = Slightly active
- pH > 4.6 = Caries inactive

Streptococcus mutans level in saliva

- **Principle:** Measures colony forming units of *S. mutans* per unit volume of saliva and from plaque samples of discrete sites such as occlusal/proximal to detect and quantify *S. mutans* on teeth.
- **Procedure:**
 - Sample is obtained by use of tongue blades. The tongue blade is pressed against *S. mutans* selective MSB (mitis salivarius bacitracin) agar.
 - Agar plates are incubated at 37°C for 48 hrs at 5 percent carbon dioxide gas.
 - Counting colonies is done with characteristic morphologies of *S. mutans* on the MSB agar plates. Colonies are counted using Quebec colony counter or with the help of microscope.

Results (Table 2.9):

TABLE 2.9: Results interpreted in *Streptococcus mutans* levels in saliva test

Sr. No.	CFU/ml saliva	Grade
1.	<10 ⁴	Light caries activity
2.	10 ⁴ -10 ⁵	Slight caries activity
3.	10 ⁵ -10 ⁶	Moderate caries activity
4.	>10 ⁶	Marked caries activity

Dip slide method for S. mutans count

- **Principle:** Estimation of *S. mutans* levels in saliva
- **Procedure:**
 - Paraffin stimulated saliva is poured on a special plastic slide coated with MSA (Mitis salivarius agar) containing 20 percent sucrose.
 - Two disks containing 5 mg bacitracin are placed on the agar 20 mm apart.
 - Slide is tightly screwed into a cover tube and incubated at 37°C for 48 hours in a sealed candle jar.
 - Dentocult SM and Cariescreen SM kits are commercially available.

Results:

- Score 1 = Low. The colonies are discrete and could be readily counted at 15x magnification with the total count of CFU inside the inhibition zones less than 200.
- Score 2 = Medium. The colonies are discrete and the number in the zone of inhibition is more than 200 visualized under 32x magnification.
- Score 3 = High. The colonies are tiny and almost completely or totally cover the inhibition zone with the number of colonies uncontrollable even with 32x magnification.

Salivary buffer capacity test

- **Principle:** This test measures no. of ml of acid required to lower the pH of saliva through an arbitrary pH interval
- **Procedure:**
 - 10 ml of stimulated saliva is collected under oil at least 1 hour after eating.
 - pH of 5 ml of saliva is adjusted to seven by addition of lactic acid or base.
 - Level of lactic acid is then added till a pH of six is reached.
 - Number of ml of lactic acid needed to reduce pH from 7 to 6 is a measure of the buffer capacity of saliva.

Results:

- A high acid buffering capacity indicates a low caries activity.
- A lower acid buffering capacity indicates a higher caries activity.

Enamel solubility test

- **Principle:** When glucose is added to saliva containing powdered enamel, organic acids are formed. These will decalcify the enamel resulting in an increase in the amount of soluble calcium in the mixture. The extent of increased calcium is supposedly a direct measure of the degree of the caries susceptibility.
- Since the equipment required is complex, this test is generally not suited for in-office procedures.
- Trained personnel are also required which makes this test uneconomical.

Salivary reductase test

- **Principle:** Measures the activity of the reductase enzyme present in salivary bacteria. Measures the susceptibility of the patient to caries.
- **Procedure:**
 - Treatex kit is available for this test.
 - Saliva is collected in a plastic container and the sample is mixed with the dye Diazo-resorcinol.
 - Color change is read after 15 mins.

Results (Table 2.10):

TABLE 2.10: Results interpreted in salivary reductase test			
Color	Time	Score	Caries activity
Blue	15 minutes	1	Non conducive
Orchid	15 minutes	2	Slightly conducive
Red	15 minutes	3	Moderately conducive
Red	Immediately	4	Highly conducive
Pink or white	Immediately	5	Extremely conducive

Alban test⁵⁸

- **Principle:** Simplified substitute of Snyder test
- **Procedure:**
 - 60 g of Snyder test agar is placed in 1 liter of water.
 - When thoroughly melted, agar is distributed using 5 ml per tube.
 - Tubes are autoclaved for 15 minutes and cooled.
 - Patient expectorates directly in the tube.
 - Tubes are incubated at 37°C for 4 days.
 - Results are recorded on the patient's charts

Scale for scoring:

- No change = 3/4
- Beginning color change (From top of medium down) = +
- One half color change (From top down) = ++
- Three fourths color change (From top down) = +++
- Total color change to yellow = ++++

The following method is used for final recordings, after 72 or 96 hours of incubation:

- Readings negative for entire incubation period are labeled “negative”
- All other readings are labeled “positive” whether +, ++, +++ or ++++.
- Slower change or less color change (compared to previous test) is labeled “improved”.
- Faster change or more pronounced color change (compared to previous test) is labeled “worse”.
- When consecutive readings are nearly identical, they are labeled “no change”.

Streptococcus mutans screening testA. *Plaque/tooth pick method*:

- *Principle*: Dilute plaque samples are screened by culturing on a selective culture medium.
- *Procedure*: Plaque samples are collected from the gingival thirds of buccal tooth surfaces, one from each quadrant and placed in Ringer's solution.
- Sample is homogenized and streaked across MSA plates.
- Incubated at 37°C for 72 hrs.
- Total colonies in 10 fields are recorded.
- Thus this test is a semi quantitative screening test for *S. mutans*.

B. *Saliva/tongue blade method*:

- *Principle*: Main difference from the plaque method is that a saliva sample is used.
- *Procedure*:
 - Paraffin wax is chewed for one min to displace plaque microorganisms.
 - Sterile tongue blade is rotated 10 times in the mouth.
 - This tongue blade is pressed into MSB agar in a petri dish and incubated at 37°C for 72 hours.
 - Number of *S. mutans* is estimated.

*Fosdick calcium dissolution test*⁵⁹

- *Principle*: Measures milligrams of powdered enamel dissolved in 4 hrs by acid formed when the patient's saliva is mixed with glucose and powdered enamel.
- *Procedure*:
 - Twenty five milliliter stimulated saliva is collected and aliquot is analyzed for calcium content.
 - Remaining saliva is placed in a test tube with 0.1 g of powdered human enamel.
 - Tube is sealed and shaken for 4 hrs at body temperature after which it is analyzed again for calcium content.
 - Amount of dissolution increases as the caries activity increases.

*Dewar test*⁶⁰

- *Principle*: Similar to Fosdick calcium dissolution test.
- Difference is that in Dewar test final pH after 4 hrs is measured and not the calcium content
- No adequate clinical correlation has been found, hence uncommonly used.

Limitations of Caries Activity Tests

- None of the tests are highly reliable as indicators of caries as it is a multifactorial disease.
- Caries activity tests provide an important but indirect evidence associating microbes with dental caries.

- Quite a few tests require lab support and may take days for the result.
- Increased chair-side time is required.
- Trained personnel are required.

CONCLUSION

The best predictor of expected caries activity results from the combined use of several selected tests, as one single test may assess only one of the contributory factors of caries, and hence may not correlate with the clinical appearance of caries.

DIAGNOSIS OF DENTAL CARIES

- Diagnosis of dental caries is fundamental to the practice of dentistry and one of the basic principles of minimally invasive dentistry.
- Numerous methods have been used to diagnose carious lesions and the past few decades have shown a tremendous revolution in this field.

VISUAL OBSERVATION (FIG. 2.22)

- Requires good lighting and dry, clean teeth.
- Any deposit of calcium or plaque present should be cleaned before attempting an accurate diagnosis.
- Each quadrant of the mouth is isolated with cotton rolls and observation is carried out with the help of a gentle blast of air from a three way syringe.
- Any changes in tooth surface texture or color are noted apart from frank cavitations.
- But this method may not be sufficient to assess the extent of decay.

TACTILE OBSERVATION (FIG. 2.23)

- Traditionally sharp probes were used to detect the tacky feel of early cavitation.
- A sharp straight, pigtail (cowhorn), curved shank or the 11/12 type explorer have been used for tactile examination of caries.
- A probe should not be used because a sharp probe can actually damage an incipient carious lesion as per the results obtained by Kühnisch J et al, 2007 in an SEM study done on intact and incipient carious tooth surfaces.⁶¹
- A probe may carry microorganisms into the lesions and facilitate spread of caries.

Kidd and Fejerskov suggest that to “jab” a sharp explorer into a lesion to determine if it is “sticky” is likely to “cause a cavity and this will encourage biofilm stagnation and lesion progression”.⁶² They emphasize that the formation of a cavity is a critical moment clinically because the biofilm is protected

Caries Assessment Tool (CAT): (Table 2.11)**TABLE 2.11:** American Academy of Pediatric Dentistry, Council on Clinical Affairs. Policy on use of a caries risk assessment tool (CAT) for infants, children and adolescents. *Pediatr Dent*, 2002; 25: 18⁵³

<i>Caries Assessment Tools</i>	<i>Low Risk</i>	<i>Moderate Risk</i>	<i>High Risk</i>
1. Clinical conditions	No carious teeth in last 24 months	Carious teeth in the past 24 months	Carious teeth in the past 12 months
	No enamel demineralization/white spot lesions	One area of enamel demineralization	More than one area of enamel demineralization
	No visible plaque; no gingivitis	Gingivitis	Visible plaque on anterior teeth
			Radiographic enamel caries
			High titers of mutans streptococci
			Wearing dental or orthodontic appliances
			Enamel hypoplasia
2. Environmental characteristics	Optimal systemic and topical fluoride exposure	Suboptimal systemic fluoride exposure with optimal topical fluoride exposure	Suboptimal topical fluoride exposure
	Consumption of simple sugars or foods strongly associated with caries initiation, primarily at mealtimes	Occasional (e.g. 1-2) between meal exposures to simple sugars or foods strongly associated with caries	Frequent (e.g. 3 or more) between meal exposures to simple sugars or foods strongly associated with caries
	High caregiver socioeconomic status	Midlevel caregiver socioeconomic status (e.g. eligible for school lunch program)	Low-level caregiver socioeconomic status (eligible for Medicaid)
	Regular use of dental care in an established dental home	Irregular use of dental services	No usual source of dental care
			Active caries present in the mother
3. General health conditions			Children with special health care needs
			Conditions impairing saliva composition/flow

**FIGURE 2.22:** Visual observation of dental caries**FIGURE 2.23:** Tactile observation of carious lesions using diagnostic instruments

in a microcavity and the cavity might have first been created by dentists using explorers. In Europe, use of an explorer to probe carious lesions is even considered unethical.

Wilkins suggested that dentists should use a blunt periodontal probe and gently run the probe over the surface with no pressure or the dental explorer can gently be used to remove biofilm or debris to assist with visualization.⁶²

RADIOGRAPHS

- The use of radiographs to examine teeth and other oral structures for the presence of oral disease remains the “gold standard”.
- Good bitewing radiographs are important in the detection of early carious lesions specially pit and fissure and proximal caries (Fig. 2.24). Suggested radiographic protocol for the pediatric patient with no previous radiographs has been outlined in Table 2.12.

The various limitations of the radiographic method are:

- The phenomenon of hidden caries/occult caries, i.e. surface hardening of tooth due to extensive use of fluorides makes it more impenetrable to exploration, while at the same time masking of the carious activity occurs just below the tooth surface and along the DEJ. In this case, tooth appears caries free clinically and/or radiographically but is found to be carious by other diagnostic means.
- Overlapping of approximal contacts.
- False diagnosis due to overestimation of lesion depth which may appear to be increased due to change in angulation.
- Occlusal lesions imperceptible because of solid buccal and lingual cusps.
- It is a two dimensional image of a three dimensional object.
- Cervical burn-out areas may mimic cervical caries.



FIGURE 2.24: Bitewing radiographs showing secondary caries (arrows) under the amalgam restoration

TABLE 2.12: Suggested radiographic protocol for the pediatric patient with no previous radiographs⁶⁴

Age (Years)	Considerations	Radiographs
3-5	No apparent abnormalities (open contacts)	None
	No apparent abnormalities (closed contacts)	2 posterior bitewings, size 0 film
	Extensive caries	4-film survey (2 bitewings, size 0 and 2 occlusal projections)
	Deep caries	Selected periapical radiographs in addition to 4-film survey
6-7	No apparent abnormalities	8-film survey
		Selected periapical radiographs in addition to 8-film survey
8-9	No apparent abnormalities or extensive or deep caries	12-film survey
10-12	No apparent abnormalities or extensive or deep caries	12 or 16-film survey, depending on patient size

Conventional Radiography⁶⁵

Conventionally, two types of techniques are employed:

- Intraoral periapical radiography and Bitewing radiography. Periapical radiographs are primarily useful for detecting changes about the root and in between the teeth. If paralleling technique is used, the usefulness of this projection is increased for detecting caries in anterior and posterior teeth. Bitewing radiographs are more important to detect incipient lesions at contact points. Also when used as adjuncts, the bitewings significantly improve the accuracy of pit and fissure caries diagnosis.

Xeroradiography

This technique simulates the photocopying machine. It is a plate coated with a layer of selenium particles. When X-rays are passed onto the film, a latent image is formed which is then converted to a positive image. The main characteristics of xeroradiographic technique are the ability to have both positive and negative prints together.

It is twice as sensitive as conventional D-speed film and a phenomenon of “Edge Enhancement” is possible. Edge enhancement means differentiating areas of different densities especially at the margins or edges. But it also has disadvantages like varying exposure time and development should be within 15 minutes.



FIGURE 2.25: Digital imaging of the carious lesion

Digital Imaging (Fig. 2.25)

Dental image acquisition for dental examinations and diagnosis has been transformed by digital imaging, also known as computerized digital radiography. Digital radiographic images are created by using the spatial distribution of pixels and the different shades of gray of each of the pixels. In other words, the digital radiographic imaging devices interface with a computer to digitize the digital radiographic image into pixels that are then viewed on a computer monitor. Rather than using traditional radiographic film, digital radiographs are taken by using a sensor that is placed in the same location that dental film would be placed. The image can be viewed on a computer monitor, stored, transmitted to a remote site, or printed. Digital imaging equipment is also available for taking panoramic and cephalometric views extraorally. It has the following advantages over traditional radiography:

- Radiation exposure of the patient is significantly reduced.
- Eliminates chemical processing and accompanying errors.
- Hazardous waste and lead foil are eliminated.
- Same film positioning, no new positioning to learn.
- Images can be transferred to other health care professionals without loss of original quality.

There are two types of nonfilm receptors for recording digital images:

1. The Digital image receptor (DIR) which collects the X-ray directly (DIRECT DIGITAL IMAGING).
2. Video camera for forming digital images of a radiograph. (INDIRECT DIGITAL IMAGING).

Digital image receptor works on a Charged couple device (CCD), which is electronically connected to a computer. CCD is a semiconductor made up of metal oxides such as silicon that is coated with X-ray sensitive phosphorus. CCD is sensitive to both X-rays and visible light. The CCD is placed intraorally and it captures image, which is stored in computer memory and can be displaced for viewing.

It also has some disadvantages:

- High cost of the system.
- The life expectancy of CCD is not fixed.

The current evidence suggests that digital systems performed comparably with film radiography for detection of dental caries.⁶⁶

Computer Image Analysis⁶⁷

Some of the researchers have developed a computer-based software system that is capable of diagnosing approximal caries and making decisions about restorative care. These softwares have been developed for automated interpretation of digital radiographs in order to standardize image assessment. Software packages like “Caries Finder” have the potential to raise overall accuracy by increasing the consistency of treatment decisions over time.

In 1984 Pitts and in 1990 Heaven and others applied such computer-based software systems for image processing and analysis of approximal caries. The researchers found that the caries finder computer system did not differ from experienced clinicians in overall accuracy of detecting approximal caries and planning restorative therapy. Image analysis systems can be an important tool in reducing the number of restorations placed in intact surfaces. The results of the computer-based caries diagnostic system were more precise. Dentists relying on a computer-based caries diagnostic system; were less likely to restore non-cavitated approximal surfaces than were dentists who did not use such a system.

Advantages:

- Observation of smaller lesions.
- It is possible to monitor the lesions.
- Quantification of small lesions is possible.

Disadvantages:

- There is always a need for standardization of exposure geometry.
- Sensitivity is higher but specificity is lesser.
- Time consuming and less economical.

Subtraction Radiography

The most important advantage that digital imaging has for dental clinicians is that it can also be used for subtraction purposes. It is a technique by which structured noise is reduced in order to increase the detectability of changes in the radiographic pattern.

It requires two identical images. The subtracted image is a composite of these two images. The ability of digital subtraction to record minimum differences depends on degree of matching of the two images. Images taken over time can be superimposed, which makes an excellent method for tracking

progress of carious lesion over time. Likewise dental hygienists can also use digital subtraction radiography to track hidden and small carious lesions to determine if fluoride applications and patient self-care are being effective in remineralizing these lesions, as more than half of shallow dentinal lesions can be arrested and so operative therapy avoided. Thus it is helpful for caries management, not just caries diagnosis.

ELECTRICAL RESISTANCE

Sound tooth enamel is a good electrical insulator due to its high inorganic content. Enamel demineralization results in increased porosity. Saliva fills these pores and forms conductive pathways for electrical current. The electrical conductivity is hence directly proportional to the amount of demineralization that has occurred. Electrical resistance is measuring the electrical conductivity through these pores.

An instrument called “Van Guard electronic caries detector” has been designed to measure electrical conductivity of the tooth. The electrical conductivity of the tooth is expressed numerically on a scale from 0 to 9, indicating change from sound tooth to an increased degree of demineralization.

Advantages

- Very effective in detecting early pit and fissure caries.
- It can monitor the progress of caries during caries control program.

Disadvantages

- It can only recognize demineralized areas and not caries specifically. The hypomineralized areas which may be of developmental origin or carious origin, will give similar type of readings.
- Presence of enamel cracks may lead to false positive diagnosis.
- A sharp metal explorer is utilized which is pressed into the fissure causing traumatic defects.
- Separate measurements are required for different sites making full mouth examination quite time consuming.

A modified form of instrument ‘Electrical Caries Monitor’ not only detects caries at a single point on the tooth but can also screen the whole of the occlusal surface for caries by covering the surface with a conducting medium before placing the probe tip.

DIAGNOSTIC METHODS BASED ON VISIBLE LIGHT

Principles of Light Transmission through Teeth

Sound enamel consists mainly of hydroxyapatite crystals which are very densely packed, giving the enamel glass-like, translucent appearance. The yellow-white color of teeth is the result of dentin shining through the translucent enamel layer.

Light that shines on a tooth will, in part, penetrate the tooth and is scattered or absorbed inside.

Scattering is the process in which the direction of photon is changed without loss of energy. Absorption is the process in which photons lose their energy, mostly by conversion into heat. Since scattering does not cause the light to be lost, scattering may occur many times consecutively along the path, a phenomenon called ‘multiple scattering’. After one or more scatter events, a photon may reach the tooth surface again and leave the tooth. Back-scatter or volume reflection is the phenomenon where photons leave through the surface by which they entered. When photons leave through another surface, the phenomenon is called diffuse transmission.

In a sound tooth, scattering is much more probable than absorption. In dentin both scattering and absorption occur more frequently along the light path than either occurs in the enamel. The whitish appearance of teeth is due to the fact that absorption is much lower than scattering.⁶⁸

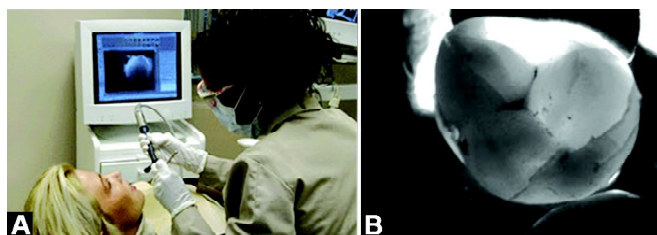
In white spot carious lesion, scattering is stronger than in sound enamel. The penetrating photons change direction more often in carious enamel and are generally back-scattered before they reach dentin. Therefore, a lesion observed in reflection appears whiter than the surrounding sound parts of the tooth. Brown lesions are due to the presence of light-absorbing material in the lesion.

A slight increase in enamel porosity leads to a change in the optical properties of enamel in such a way that light is increasingly scattered. This is presumed to be primarily due to the fact that the remaining small mineral particles in the lesion are embedded in water rather than in mineral rich sound enamel thereby increasing the difference in refractive index between the scattering photon and its environment.⁶⁹

The refractive index (RI) of enamel apatite is 1.62, and RI of water and air is 1.33 and 1.0, respectively. Thus, when the pores of white spot enamel lesion are filled with water, the light scattering is less than when the lesion is dry and the pores are filled with air. After dehydration of a caries lesion in enamel, the lesion looks whiter, as a result of more scattered light, because of the larger difference in RI, 1.62 versus 1.0

Optical Caries Monitor

White spot lesions look whiter than the surrounding sound enamel because of the strong scattering of light within the lesion. This stronger scattering can be quantified with methods based on fiber technology. The measured quantity is the ‘scattering coefficient.’ An instrument for clinical use, the optical caries monitor was constructed comprising a light source, measuring and reference units and a detection part. The light is transported through a fiber bundle to the tip of the handpiece. The tip is placed against the tooth surface and the reflected light is collected by different fibers in the same tip.



FIGURES 2.26A and B: Placement of fiberoptic transillumination probe on the fissure area and the image formed by the device on the computer screen

The scattering coefficient values are correlated with histological picture, lesion depth and with mineral loss per unit area of the lesion surface at the deepest point of the lesion.

The optical caries monitor can be used only for the quantification of caries lesions on smooth surfaces. After further development for clinical application the method may be useful, e.g. for quantitative evaluation of the regression of smooth surface enamel lesions developed during fixed orthodontic therapy.

Fiber Optic Transillumination (Figs 2.26A and B)

Fiber Optic Transillumination (FOTI) works on the principle that since a carious lesion has a lowered index of light transmission, an area of caries appears as a darkened shadow that follows the spread of decay through the dentin. FOTI has been used in common medical procedures since 1960. In dentistry, it was first used as an improved light source for surgical retractors. In 1970, Friedman and Marcus suggested the use of FOTI in detection of carious lesions.⁷⁰

It has been introduced as a quantitative diagnostic method by which teeth are transilluminated. Fiber optic consists of a halogen lamp and a rheostat to produce a light of variable intensity. The 150-watt lamp generates a maximum light intensity of 4000 lx at the end of a 2 mm diameter cable. Two attachments are used; a plane mouth mirror mounted on a steel cuff and a fiber optic probe 0.5 mm in diameter so that it can be placed in the embrasure region. It produces a narrow beam of light for transillumination. The rheostat is set to give a light of maximum intensity. For examination, the tip of the probe is placed in the embrasure immediately beneath the contact point of proximal surface to be examined either on the buccal or lingual surface depending on the tooth. The marginal ridge is viewed from the occlusal surface.

The shadow extending to the dentino-enamel junction beneath the marginal ridge may be evident if there is a break in the integrity of the enamel of marginal ridge.

Compared with radiography, the technique is simple and fast. The majority of clinical studies comparing diagnosis with FOTI or unaided clinical diagnosis use radiography as a gold standard. Sensitivity values, that is the ability to detect caries,

and specificity values, that is the ability to detect sound surfaces vary considerably in the studies. For permanent teeth, the sensitivity of FOTI varies from <50 to 85 percent, while the specificity is generally high, >95 percent.⁷¹

Advantages

1. No hazards of radiation.
2. Simple and comfortable for patients.
3. Lesions, which cannot be diagnosed radiographically, can be diagnosed by this method.
4. Not time consuming.

Disadvantages

1. Permanent records are difficult to maintain as can be kept in radiographs.
2. It is subject to intra and inter observer variations.
3. Difficult to locate the probe in certain areas.

Digital Imaging Fiberoptic Transillumination

Transillumination has long been used in dental hygiene for the detection of carious lesions and especially calculus for over 30 years. The Digital imaging fiberoptic transillumination (DIFOTI) system has elevated traditional transillumination to more sophisticated diagnostic levels. The DIFOTI allows for images taken from all tooth surfaces to be digitally captured by using a digital charged couple device camera and sent to a computer for analysis with dedicated algorithms. The images are stored for longitudinal evaluation of carious lesions. When teeth are transilluminated, the areas of demineralization in enamel or dentin scatter light, and incipient caries appear as darker areas in the captured images (Fig. 2.27). The DIFOTI varies from the DIAGNOdent in that it has two handpieces, one for smooth surface caries detection and one for occlusal caries detection. The system uses a disposable mouthpiece and foot control that allows for selecting the image of concern and a computer for capturing and storing the images. Like the QLF and DIAGNOdent, the DIFOTI can be used for preventive management of early carious lesions, and the information gleaned can be used by the dental hygienist to assist patients in targeting at risk areas in the mouth. The DIFOTI does not have the capability to determine depths of lesions, but unlike other alternative caries detection devices, it can detect caries on interproximal surface as well as radiographs can.

PULSED LASER CARIES DETECTOR—DIAGNODENT (FIG. 2.28)

DIAGNOdent is a battery-powered device that relies on laser fluorescence to detect caries. The dentist places the tip of diagnostic probe on the surface of the tooth. A pulsed laser beam with a wavelength of 655 nm is then transmitted on the tooth surface through the probe as it scans along the pits and fissures. When the penetrating laser beam encounters the

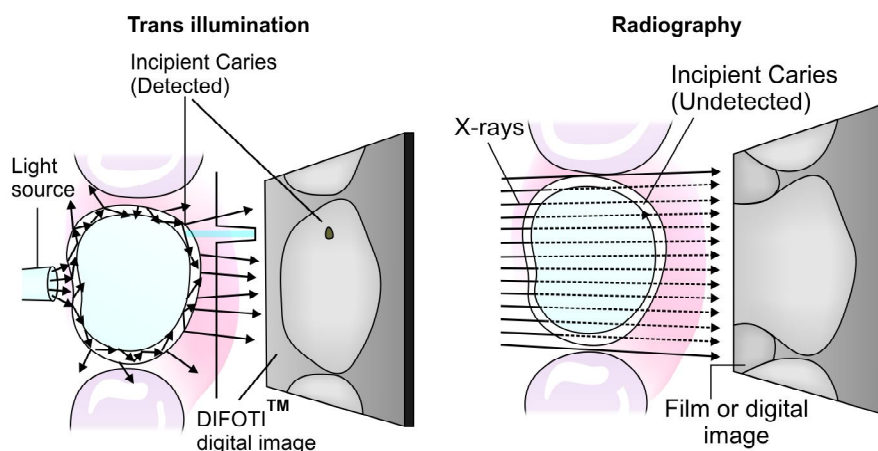


FIGURE 2.27: Differentiating features in images using DIFOTI and conventional radiography

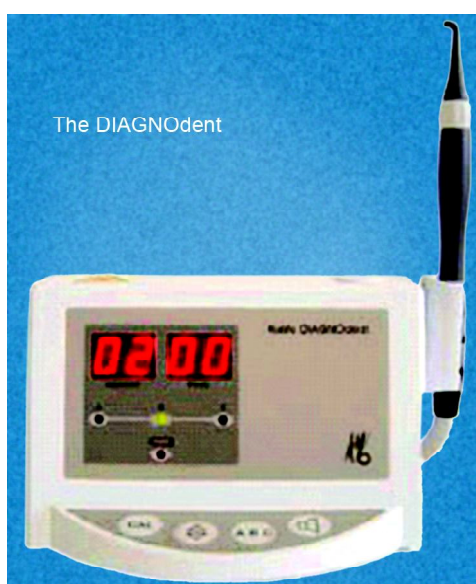


FIGURE 2.28: Processing of pulsed laser caries detector

presence of carious tooth structure, fluorescent light with an altered wavelength is stimulated. An acoustic signal is set off as the new wavelength of light is translated back to the power box, and a numeric reading appears on the monitor.

After calibration, the appropriate probe is selected. For smooth surfaces, the probe is gently run over the surface of the tooth. For occlusal examinations, the probe should be moved (e.g. mesially to distally) and swayed buccolingually to ensure that all fissures are examined. The device displays the results in real time. The unit presents current and peak values from the time when the unit was last reset. Therefore, the unit should be reset between teeth, so that the peak value for each tooth can be recorded, along with notes as to the location on the tooth where the reading was taken. Further

readings at recall appointment can be used to determine if the DIAGNOdent value has increased, decreased or stabilized.⁷²

Processing (Fig. 2.29)

When the light is absorbed it induces infrared fluorescence of organic and inorganic materials. This fluorescence is collected at the top of the handpiece and transmitted back to the DIAGNOdent unit. The fluorescence is converted into an acoustic signal and displayed as an integer that ranges from 0-99. An increase in fluorescence is indicative of carious tooth substance, particularly when the displayed reading is 20.⁷³

Principles of Laser/Light induced Fluorescence

Laser light is composed of electromagnetic waves with equal wavelengths and equal phases. Some materials possess the characteristic of fluorescence when illuminated with light. Fluorescence is a phenomenon by which the wavelength of the emitted (original) light is changed into a larger wavelength upon reflectance. When the emitting light is from the visible spectrum, the fluorescent light has different color to the emitting light. By using a filter through which only fluorescent light can be passed, the intensity of the fluorescent light can be measured. The intensity of the fluorescent light is proportional to the amount of material that causes the fluorescence. The fluorescence of dental hard tissues has been known for a very long time. Three types of fluorescence can be distinguished: blue fluorescence is excited in the near ultraviolet, yellow and orange fluorescence is excited in the blue and green, and red fluorescence in the far red and near infrared.

Dental enamel and dentin possess the characteristic of fluorescence and this natural fluorescence is called auto fluorescence. Caries lesions, plaque and micro-organisms also contain fluorescent substances. The difference between the fluorescence of sound tooth tissues and that of caries lesions can

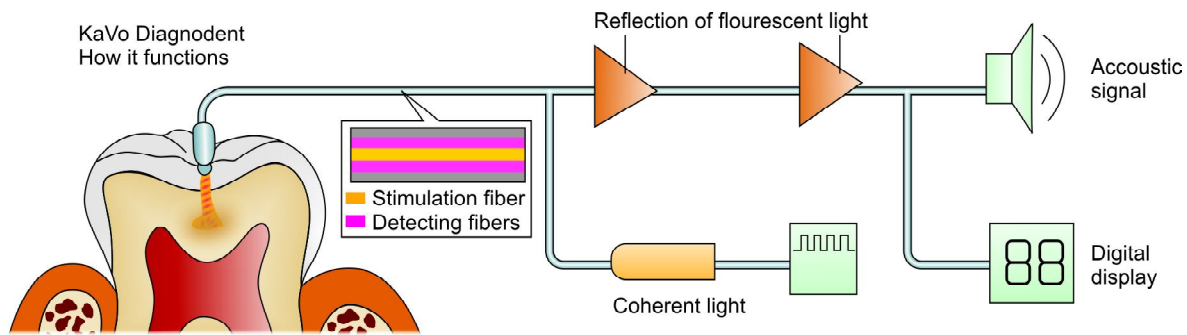


FIGURE 2.29: Pulsed Laser Caries Detector (DIAGNOdent)

be made visible by the Quantitative laser or light induced fluorescence (QLF) method. The measurement of the fluorescence caused by a caries lesion yields a quantitative diagnosis.

The chromophores causing the fluorescence of dental hard tissues are not clearly identified. The blue fluorescence was assigned to dityrosine. It seems likely that most of the yellow fluorescence stems from proteinic chromophores, which probably cross-link between chains of structural proteins. The red infrared fluorescence has been assigned to protoporphyrin which is present as a bacterial breakdown product.

Interpretation of Results

The numerical scale readings can be interpreted as:

- 0 to 14—No caries or histological enamel caries limited to the outer half of enamel thickness.
- 15 to 20—Histological caries extending beyond the outer half, but confined to the enamel.
- 21 to 99—Histological dentinal caries.

DIAGNOdent is more so helpful in diagnosing “occult or hidden” caries.

Limitations

- The depth of penetration of the light is limited to about 2 mm.
- The value of the device lies only in detection of occlusal involvement; it will not identify interproximal caries.

ULTRAVIOLET ILLUMINATION

Ultraviolet light (UV) has been used to increase the optical contrast between the carious region and the surrounding sound tissue. The natural fluorescence of tooth enamel, as seen under UV light illumination is decreased in areas of less mineral content such as in carious lesions, artificial demineralization or developmental defects. The carious lesion appears as a dark spot against a fluorescent background.

Advantages

It is a more sensitive method than the visual-tactile method.

Disadvantages

- The specificity is a problem between the carious lesion and the developmental defect.
- Still this method has not been developed into a qualitative method.

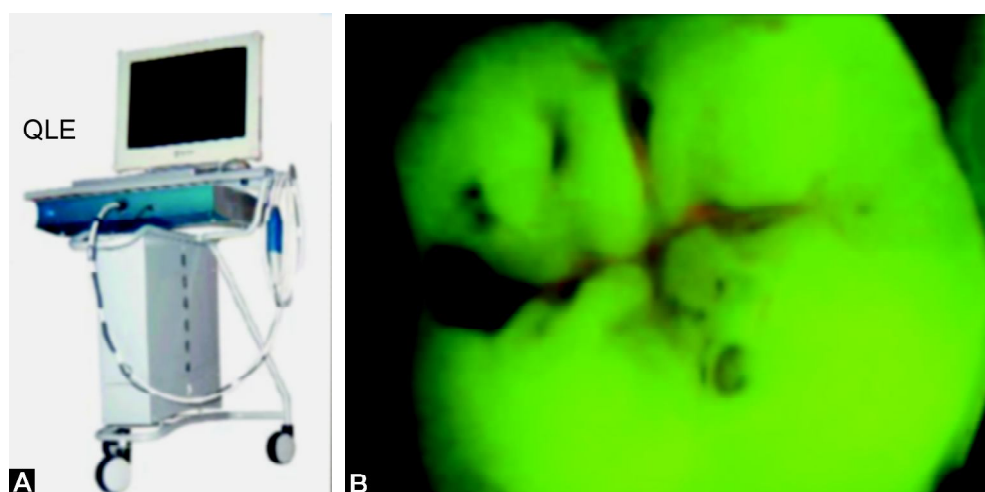
QUANTITATIVE LIGHT-INDUCED FLUORESCENCE⁷² (FIGS 2.30A and B)

Quantitative light induced fluorescence (QLF) enhances early detection of carious lesions, particularly progression or regression of white spots of smooth surface lesions. QLF uses the intrinsic fluorescence of the teeth within the yellow-green spectrum of visible light. The tooth is illuminated with a blue light that is emitted from a handpiece and causes the tooth structure to fluoresce and the image is captured with a color microvideo charged couple device camera. The data are then stored and analyzed by image analysis computer software (Inspektor Dental Care, Amsterdam, The Netherlands). The tooth is seen on the computer monitor as fluorescent green; dark areas indicate mineral loss. With the computer software, the image can be saved and compared over time to track demineralization or remineralization.

QLF is a useful method for visualizing dental biofilm that is not visible clinically under ordinary lights. It also serves as an evaluation tool to assess the outcome of preventive self-care plans developed for the patient.

ENDOSCOPE/VIDEOSCOPE

The technique is same as that of QLF. In this, tooth is illuminated with blue light in the range of 400 to 500 nm. Similarly, a white light source can be connected to an endoscope by a fiber optic



FIGURES 2.30A and B: Quantitative light fluorescence device and the detection of carious lesion by fluorescence light

cable so that teeth can be viewed without a filter. This technique is referred to as white light endoscopy.

Additionally, a camera can be used to store the image. The integration of the camera with the endoscope is called a videoscope. A miniature color video camera is mounted in a custom made metal mirror holder. This is designed in such a way that the image of the surface of enamel can be viewed directly over a television screen.

Advantages

- It provides a magnified image.
- Clinically feasible.

Disadvantages

- Requires meticulous drying and isolation of teeth.
- Time consuming.
- Very costly.

ULTRASONIC IMAGING

Ultrasonic imaging was introduced for detecting early carious lesions in smooth surfaces. Ultrasound used in ultrasonography is a sound wave with a frequency ranging from 1.6 to about 10 MHz. Its diagnostic purpose is to delineate, depict and measure organs and tissues in the body. In medicine ultrasound is used to create images of internal organs. These images are produced when the sound waves are directed at the organs of the body and then reflected back to a scanner which measures them. Ultrasound interacts differently with different types of tissue. The interaction depends upon the acoustic properties of the tissue, such as the attenuation, absorption and scattering,

impedance and velocity. Acoustic parameters depend strongly on the frequency of the ultrasound as well as other parameters such as temperature.

In dentistry, ultrasound was first used by Ng et al 1988, to image the tooth and to find caries lesions on smooth surfaces of teeth. It was concluded from this initial study that although small lesions could be detected, the method was inappropriate to apply to patients. Moreover, it is not possible to detect shallow caries lesions. It is observed that there is a definite correlation between the mineral content of the body of the lesion and relative echo amplitude ranges. The sites with a visible cavitation produce echoes with substantially higher amplitude. This method is more sensitive than visual-tactile method; however it is not a quantitative method.

DYE PENETRATION METHOD

Dye can visualize a subject from its routine background or if several objects have a similar appearance, coloring by a dye may discriminate between them and allow identification. Dyes should fulfill the following criteria before being recommended for clinical use:

- Dyes should be absolutely safe for intraoral use.
- Dyes should be specific and stain only the tissues they are intended to stain.
- Dyes should be specific and easily removed and not lead to permanent staining.

Dyes for Detection of Carious Enamel (Fig. 2.31)

- 'Procion' dyes stain enamel lesions but the staining becomes irreversible because the dye reacts with nitrogen and hydroxyl groups of enamel and acts as a fixative.



FIGURE 2.31: Caries detector dye

- ‘Calcein’ dye makes a complex with calcium and remains bound to the lesion. ‘Fluorescent dye’ like Zyglo ZL-22 has been used *in vitro* which is not suitable *in vivo*. The dye is made visible by ultraviolet illumination.
- ‘Brilliant blue’ has also been used to enhance the diagnostic quality of fiberoptic transillumination.

The use of dyes for diagnosing enamel lesions cannot be used clinically as yet. If possible it will thus allow remineralization.

Dyes for Detection of Carious Dentin

Histopathologically, carious dentin is divided into two layers—outer layer of decalcification, which is soft and cannot be remineralized and the inner decalcified layer, which is hard and can be remineralized. Dyes have been tried to differentiate between these two zones of dentin caries. 0.5 percent basic fuchsin in propylene glycol has proved to be successful for this purpose. Thus, it is possible to remove completely the outer carious zone in dentin caries as it contains denatured collagen.

Basic fuchsin dye was considered to be cariogenic; therefore, it has been replaced by acid red and methylene blue. Methylene blue is also slightly toxic so acid red is preferred.

A Modified Dye Penetration Method

The Iodine penetration for measuring enamel porosity of an incipient carious lesion was developed by Bakhos et al, 1977.⁷⁴ Potassium iodide is applied for a specific period of time to a well-defined area of enamel and thereafter the excess is removed. The iodine, which remains in the micropores, is estimated and that indicates the permeability of enamel.

To apply this method for caries diagnosis remains a complicated procedure, because for each type of acid attack, a separate calibration under the same condition is needed.

Disadvantages of Caries Detector Dyes

- Not all dye stainable dentin is infected.
- The absence of stain does not ensure elimination of bacteria.
- The dyes stain the organic matrix of less well-mineralized dentin.
- Caries detector dye lacks specificity.
- The dyes neither stain bacteria nor delineate the bacterial front but stain the collagen associated with less mineralized organic matrix
- Many dyes, such as procion dyes, produce irreversible staining that is clinically unacceptable.

CONCLUSION

None of these methods of detection is infallible, and none of them justifies immediate surgical intervention. Each technique has a place in diagnosis, but, in view of the relatively slow progress of the typical carious lesion, an early lesion should be treated with caution. Surgical intervention can only be properly justified for elimination of actual cavitation.

CARIES RISK ASSESSMENT

Only in the absence of disease the restorative dentistry will succeed. That's why control is the primary focus. Correct diagnostic procedures, i.e. Caries Risk Assessment must be carried out for any at risk patient to determine patient's present and future dental health, with an understanding of the need for preventive or surgical intervention.

Caries risk may be defined as the probability that a specific number of new lesions will develop and/or a specific number of existing lesions will progress over a specific period of time.⁷⁵

The combination of careful visual assessment, patient's factors (e.g. caries risk), and the appearance of a possible lesion on radiographs is the next level of caries diagnosis, especially in instances of increased caries infection.⁷⁶

There are two reasons for assessing caries risk in the current era of reduced caries prevalence:

1. To direct individually based preventive measures to the highest risk persons who benefit most from prevention.
2. To identify low risk patients in order to delay restorations and prevent unnecessary surgical intervention.

EXAMINATION

A thorough oral examination should assess the extent and location of incipient lesions, cavitated lesions and restorations.

It should include an assessment of the activity status of the lesions and condition of the restorations.

The following evidence should be carefully gathered and recorded:

- Coronal surface:
 - Color
 - Translucency
 - Cavitation
- Root surface
 - Texture
 - Color
- Radiographs
 - Cavitation
 - Pulp
 - Alveolus
- Transillumination
 - If possible
- Electronic caries detection
 - If possible

PATIENT'S HISTORY

It is necessary to take into account the wider range of historical evidence, including the current status of the major etiological factors, before deciding if an incipient lesion is able to be arrested or will progress to cavitation. The following information should be obtained:

- A thorough history of caries, timing when restorations were placed and frequency of repair or replacement.
- An outline of present and past dietary patterns, in particular frequency of refined carbohydrate intake and consumption of acid drinks or foods.
- Past and present fluoride contact, both systemic and topical.
- Medical or social factors that may affect dental health; for example, drugs that may affect salivary flow or that contain high concentration of sweetening agents.
- Physical or medical problems that may impair a patient's ability to carry out oral hygiene or that exerts control over their diet.
- Emotional or other factors resulting in high levels of stress.
- Illness or organic problems or medications that result in frequent gastric acid regurgitation.
- Parental dental history. Most children appear to acquire the microorganisms from their mothers.

PREVENTION OF CARIES

- Stopping or reducing between meal consumption of carbohydrates, or substituting noncariogenic artificial sweeteners, e.g. sorbitol, xylitol or lycasin.
- Making the tooth structure less soluble to acid attack by using fluorides.

- Using sealants to protect susceptible areas of the tooth that cannot be kept plaque free by routine oral hygiene measures.
- Reducing cariogenic flora so that even in the presence of sucrose, acid production will be minimal, e.g. oral hygiene aids, antimicrobial agents.
- Replacement of cariogenic bacteria by low virulence mutants of streptococci that are deficient in lactate dehydrogenase or glucosyl transferase.

MANAGEMENT OF CARIES

Remineralization of early lesions

Restoration

Pulp treatment:

- Indirect pulp capping
- Direct pulp capping
- Partial pulpotomy in permanent teeth
- Vital pulpotomy
- Non-vital pulpotomy
- Partial pulpectomy in permanent teeth
- Pulpectomy in primary teeth
- Apexogenesis and Apexification

REMINERALIZE EARLY LESIONS⁷⁷

Remineralization should be recognized and utilized as far as possible for any tooth that has been subject to attack by caries, because there is no real substitute for natural tooth structure.

Successful remineralization requires intensive patient education and cooperation. Use of fluoride containing dentifrices and mouth rinses has been proven to enhance the rate of remineralization of teeth. Mineral will recrystallize in partially demineralized enamel when fluoride, calcium and phosphate ions are present in adequate proportions.

The major shortcomings of currently available toothpastes, mouth rinses and topical applications are the fact that their ability to remineralize enamel is limited by the low concentration of calcium and phosphate ions in saliva. This can be overcome by the use of newer approaches to remineralization which include:

Amorphous Calcium Phosphate
(a more soluble form of calcium phosphate)

It acts as a useful supplement to the calcium and phosphate ions present in saliva.

Casein phosphopeptides (CPP) are naturally occurring molecules which are able to bind calcium and phosphate ions and stabilize amorphous calcium phosphate (ACP). Under acidic conditions, CPP are able to release calcium and phosphate ions and thereby maintain a state of supersaturation with respect to tooth enamel, reducing demineralization and enhancing remineralization (Reynolds 1997).⁷⁸ The delivery



FIGURE 2.32: GC tooth mousse used for remineralizing incipient lesions

of CPP or complexes of CPP-ACP to the plaque fluid can be achieved by a range of vehicles, including chewing gums, dentifrices and topical gels. CPP binds well to dental plaque, and is able to slow or prevent the diffusion of calcium ions from enamel during episodes of acid challenge, and serves as a source of calcium for subsequent remineralization.

GC Tooth Mousse (Fig. 2.32)

A water based, sugar crème containing CPP-ACP (Casein Phosphopeptides—Amorphous Calcium Phosphate) which binds tooth surfaces to biofilms, plaque, bacteria, hydroxyapatite and surrounding soft tissue localizing bio-available calcium and phosphate. Saliva enhances the effectiveness of CPP-ACP and flavor helps stimulate saliva. It provides extra protection for teeth. Neutralizes acid challenges from acidogenic bacteria in plaque and other internal and external acid sources. It also promotes fluoride uptake.

Chewing Gum

A healthy adult produces around 500 ml of saliva per day. For most of the day the unstimulated flow rate is low (about 0.2-0.4 ml/min), but saliva can be stimulated by masticatory or gustatory activity. Saliva can be stimulated by any food or drink, but the most practical way of stimulating saliva is by chewing Orbit sugarfree gum. The concentration of ions (calcium and phosphate) which make up the lattice structure of hydroxyapatite are higher in stimulated than in unstimulated saliva. Consequently, stimulated saliva is more effective at remineralizing enamel crystals damaged by initial caries attack.

The other benefits of sugar-free gum are:

- Neutralization and buffering of plaque acid.
- Oral clearance of sugars, acids and food debris from the mouth.

The use of sugar-free gum after eating meals and snacks promotes the *in vivo* remineralization of enamel lesions, and

has been shown to reduce clinical caries development- in one study by up to 40 percent.

Shen P et al 2001, found that Recaldent Gum containing Xylitol and CPP-ACP has enhanced enamel remineralization considerably, compared to sugar-free chewing gum due to incorporation of CPP-ACP complexes.⁷⁹ Recaldent was invented by Professor Eric Reynolds from Melbourne University.

Use of Xylitol

It is a nonfermentable sweetener and may possess some properties that promote remineralization. In September 1890, the German chemistry professor Emi Herman Fischer and his assistant Rudolf Stanel, separated from beech chips a new compound which was named Xylit, the German word for Xylitol (Makinen, 2000).⁸⁰

Xylitol is a naturally occurring polyol which is taken up by *streptococci* but not fermentable. Habitual consumption of xylitol in the diet appears to select for *mutans streptococci* with impaired adhesion properties, i.e. they bind poorly to teeth and shed easily from plaque to saliva. Thus, it can be speculated that the streptococci of mothers in xylitol group had impaired adhesion property leading to reduced mother-child transmission of *mutans streptococci*. Use of xylitol chewing gum can retard return of oral *mutans streptococci* after suppression of these cariogenic organisms.

A recent clinical trial demonstrated that chewing a Xylitol gum three times daily for a minimum of five minutes each time for three months resulted in a ten fold reduction in salivary levels of *mutans streptococci*.

Use of Polymeric Coatings

A new technology currently under development for increasing tooth resistance to decay is the fabrication of thin polymeric coatings over tooth crowns and accessible root surfaces. According to Mandel, 1996, current research envisions a two stage process. The initial stage would be application of monomer with a controlled degree of water solubility that would allow a penetration into hydrated organic material and adhere to the tooth substance by chemical bonds. A polymeric top coat would then enhance durability and aesthetics.⁸¹

Laser Light

The ability of laser light to alter the surface of enamel and increase its resistance to acid challenge has been known for 30 years. A recent study has shown that on use of CO₂ laser light, it is efficiently absorbed by tooth minerals, is transformed rapidly into heat and forms a ceramic like surface that is highly resistant to acid attack, as well as to the initiation of caries as demonstrated in an *in vitro* model system.⁸²

TABLE 2.13: Classification of various tooth-cutting techniques

Category	Techniques
Mechanical, rotary	Handpiece and burs
Mechanical, non-rotary	Hand excavators, air abrasion, air polishing, ultrasonics, sonoabrasion.
Chemicomechanical	Caridex, carisolv, enzymes
Photo-ablation	Lasers

RECENT MODALITIES OF CARIES REMOVAL

There are many techniques available for cutting tooth tissues (Table 2.13). Some claim to remove demineralized dentin selectively whereas others are not able to make this distinction and indeed, may not even be able to remove softened tissue effectively.

The ideal cutting instruments should fulfill certain factors to satisfy both operator and patient. These factors might include:

- Comfort and ease of use in the clinical environment.
- The ability to discriminate and remove diseased tissue only.
- Being painless, silent, requiring only minimal pressure for optimal use.
- Not generating vibration or heat during operation.
- Being affordable and easy to maintain.

Excavators, Handpieces and Burs (Figs 2.33A and B)

Small round burs

They provide a conservative preparation with good explorer access and require no learning curve.

They are slow and inefficient in cutting through enamel.

Excisional biopsy burs

- The fissurotomy burs are specially designed for recontouring the fissures and accessing decay with minimal enamel removal.
- They are fast cutting, conservative and inexpensive.
- No local anesthesia is required.
- The use of the fissurotomy burs is limited to pits, fissures and grooves, however, not indicated for treatment of larger decay.
- The head length of the bur is 2.5 mm, to limit the bur tip to cut just below DEJ, and not further into the dentin.
- The tapered shape of the bur allows the cutting tip to encounter very few dentinal tubules at any given time and has been designed to minimize heat build-up and vibration.
- These burs have been designed anatomically to enlarge the fissure and eliminate small caries without removing excessive healthy enamel or dentin.

**FIGURES 2.33A and B: Caries excisional burs**

Air Abrasion

Air abrasion is an excellent tool for the minimally invasive dentist. Air abrasion cavity design preparation in combination with the wide range of currently available low viscosity adhesive materials forms an ideal alliance for minimally invasive dentistry. Air abrasion is an old dental technology that is finding a new place in modern, science-based dentistry.

Principle: It utilizes kinetic energy or inertia as a means of rapidly removing tooth structure by incorporating a fine abrasive material in a high velocity gaseous propellant.

Evolution: As early as 1945, Dr RB Black conceived the concept of application of kinetic energy in the field of dentistry. Before the invention of air and water turbine hand-piece, “Abrasive Technique” was developed primarily to minimize patient discomfort. “Air Dent Machine” by SS White Technologies was the first original air-abrasion unit based on Black’s work. The original technique has now been modified and improved as Kinetic cavity preparation (KCP) system.⁸³

In the early fifties “Abrasive technique” received considerable interest, but was never popular due to drawbacks like limited area of good vision, lack of tactile sensation, inability to achieve precise margins and angles (to suit the materials available) and possible ill effects of inhalation of abrasive particles, etc. In the early sixties, the cavity cutting procedures were precise and followed the principles of mechanical retention and resistance as amalgam and gold were the main restorative materials. The development of “Acid Etch Technique” by Buonocore in 1955 and “Composite Resin” by Bowen in 1962 revolutionized the concepts of Conservative dentistry. Recently, the paradigm shift towards minimal invasive techniques has revived the interest in air abrasion.

Components of KCP unit

- Precision-built device containing a source of suitable gaseous propellant and means of regulating the pressure
- Reservoirs for containing abrasive materials
- Hand-piece with tips made of sintered tungsten carbide with variable inner diameter

- Foot control for activation of the machine
- Other components like cabinet, gauges and dials for controls, a suction hood, etc.

Abrasive particle: The most commonly used material is Aluminium oxide. Magnesium Carbonate (Dolomite) is used, though more for prophylaxis, as it is soft and has less weight.

Aluminium oxide: 27 μm —Intraoral use, comfortable, moderately effective cutting

Aluminium oxide: 50 μm —Suitable for coarse surface finishing and extraoral microetching procedures.

Propellant: Compressed air is usually used, but it is not free from moisture. Carbon dioxide gas is the propellant of choice.

Carbon dioxide—Average pressure: 700-1300 psi, reduced to 45-80 psi at the tip.

Flow of gas: 1/3 cubic foot/minute

Recommended propellant pressure

- Cutting enamel: 80 to 90 psi
- Cutting dentin: 40 to 60 psi
- Stain removal: 40 to 60 psi
- Calculus removal: 80 to 90 psi

Pressure at 80 psi is considered to be the threshold for sensitivity. So it demands extra caution when using pressures 80 psi or above.

Nozzle diameter: The inner diameter ranges from 0.011 to 0.032 inch. The following are commonly used:

- 0.018 inch (Removal of large lesions, results in wide cone shaped cavity)
- 0.014 inch (Universal use, removal of small lesions)
- 0.011 inch (For precise cutting, preparation of occlusal pits and fissures, produces narrow deep cavity with nearly vertical walls)

Nozzle distance from tooth surface: It also directly influences the shape of the cavity as well as the amount of hard tissue removed.

- 0 to 2 mm—Cavity has nearly vertical walls. The diameter of the cavity remains approximately the same as the nozzle bore.
- 2 to 5 mm—Cavity is more conical.

TABLE 2.14: Amount of enamel removed using air abrasion

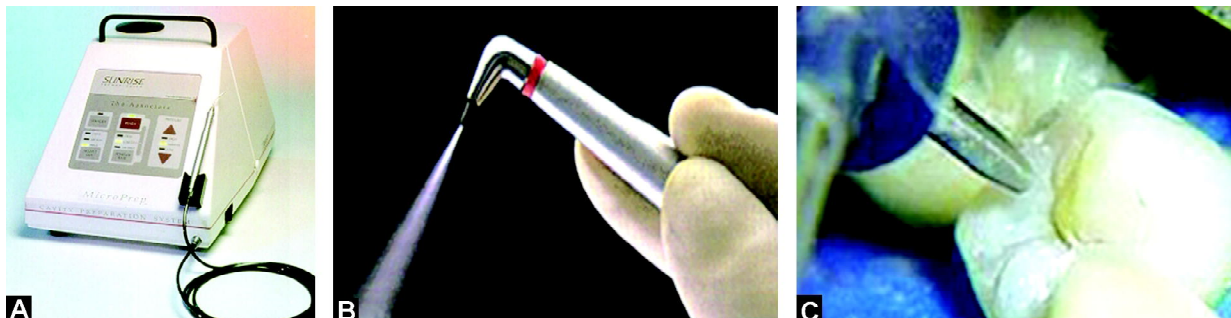
Nozzle tip distance (mm)	Amount of Enamel removed (mg)
3	12
9	25
11	30
15	28

Amount of enamel removed (50 psi, 0.45 mm diam, 30 sec): See Table 2.14

Technique (Figs 2.34 A to C)

- A setting of 80 psi or less, with 27 μm particle size and 0.014 inch tip is comfortable and adequate for most procedures.
- Clean the surface of the tooth and place a caries detection dye.
- Place the tip of the nozzle at a right angle and no more than 1 mm to the surface.
- Start with a three seconds burst to trace out grooves, fissures and pits. The burst should be interrupted over areas of sound enamel.
- Observe, diagnose and remove any remaining decay. Use short bursts to remove the last stains.
- As penetration becomes deeper, shorter burst with less air pressure may be used for patient comfort.
- Stop frequently, observe, diagnose and proceed.
- Soft, carious dentin absorbs and scatters the particle stream; the use of small round bur is recommended for the soft decay.
- Most cavity preparations take between 30 seconds to 1.5 minutes.
- Standard saliva ejector or high volume intraoral evacuator should be used.
- For additional powder control 4 $\times$ 4 gauze may be placed in the operative field.

Patient comfort: Air abrasion is generally well tolerated by the patients. Most procedures can be performed without the use of local anesthesia. If discomfort is encountered in deeper



FIGURES 2.34A to C: Air abrasion technique

preparations, the use of smaller particle size and lower pressure is more comfortable for the patient. The use of warm water spray has been advocated to maximize patient comfort. Most cavity preparations take between 30 seconds to 1.5 minutes. For longer procedures, some patients may experience discomfort from dryness and may wish to have their mouth rinsed with the water syringe and evacuated with saliva ejector.

Spray may be minimized by placing a wet 4×4 or 2×2 gauze square on the tongue and replacing it as necessary.

Precautions

- Do not touch the surface of the tooth with air abrasion tip.
- Do not back up more than 2.5 mm from the surface.
- Do not blast the whole surface from far.
- Do not sweep the tip like a brush.
- Emphysema (air embolism) is a possible complication of all dental treatment, including air abrasion; therefore never direct the particle stream into an open pulp chamber or into the gingival sulcus.
- Prior to intraoral use, development of skill is essential on extracted teeth using caries detecting dye.

Indications

- Strongly recommended for sealant therapy.
- Treatment of suspicious pit.
- Removal of old composite or amalgam fillings and fractured porcelain facings.
- Removal of high points on crown.
- Removal of casting irregularities and modification or correction of the surface that will receive porcelain (50 μ m particle size).
- For prophylaxis.

Contraindications

- Severe dust allergy.
- Asthma.
- Chronic pulmonary disease.
- Recent extraction or surgical procedure including periodontal surgery.
- Any open wound, lesion or sore, or sutures in the mouth.
- Sub-gingival caries removal.

Dynamics of air abrasion: Many factors are involved in developing particle air stream, all conforming to the laws of physics. As the airflow progresses towards the hand-piece, the decrease in inner diameter of the delivery tube generates an increase in the velocity of the particle stream. The particle stream does not reach full velocity until it leaves the tip of the nozzle by amount of 0.75 mm. When using smaller nozzle (e.g. 0.014 inch), the particle stream typically becomes supersonic and can reach twice-supersonic speeds. The stream begins to slow at approximately 1 mm past the nozzle. The particle stream is a divergent stream. It varies from a collimated stream.

Consequently the stream spreads at approximately 22° as it exits the nozzle. At approximately 4 or 5 mm past the nozzle, the stream becomes too disorganized and carries insufficient energy to act as a cutting mechanism. A common complaint of newcomers to the practice of air abrasion is that the instruments will not cut. The three most common reasons could be:

- Failure to put the nozzle near the surface to be cut—Holding the nozzle too far will only etch and abrade the wide area of surface.
- Failure to hold the nozzle steady—The natural tendency is to wave the hand-piece. For cutting to begin, the particle stream must first cavitate the surface to be cut.
- Failure to use magnification—The dentist simply cannot see the micro preparations initiated by the particle stream.

Safety of KCP: Laboratory tests show that the amount of alumina inhaled by the dentist and/or auxiliaries in an office setting to be below detectable limits. The patient inhales just 7 micrograms of alumina during each minute of treatment time. At that rate, patient would have to undergo 11.43 minutes of continued KCP to inhale an amount of alumina equal in weight to a grain of table salt (80 micrograms). That exposure time is equivalent to 28 typical 20 to 30 second KCP preparations.

Further, the patient would have to undergo as many as 3.401 KCP treatments daily to inhale the amount of alumina particles that a worker breathes daily in an environment considered safe by Oral safety health administration (OSHA) and American conference of government industrial hygienist (ACGIH).

Sonic Oscillating Systems

The Sonic oscillating systems (SONICSYS) have been developed for cutting and finishing of proximal “mini” cavities using an air driven oscillating hand-piece and partially diamond-coated working tips (JG Mount, 2000).⁸⁴ This preparation method appears to be particularly suitable for cutting small, first intervention cavities in proximal surfaces with minimal extensions and good marginal morphology, without any risk of damaging adjacent teeth.

Enamel in the proximal and gingival walls of posterior cavity preparations for restoration with composite resin preferably should be beveled, because the direction of the prisms is perpendicular to the surface. However, when using rotary instruments, much damage can be inflicted to the adjacent tooth. Proximal bevels are therefore usually omitted in small box and slot preparations. The introduction of one-sided torpedo-shaped diamond tips in a sonic device allows for beveling of proximal margins without this risk. When compared to hand instruments, the sonic tips allow for significantly better finishing of proximal bevels. The hemispherically shaped tip provides a minimal access opening to approximal cavities. After access to the lesion is achieved, caries removal is done with a round bur (low speed).

The one-sided sonic tips are excellent tools to finish and bevel margins in otherwise inaccessible areas in the close vicinity of adjacent surfaces.

Chemomechanical Caries Removal

Beeky et al 2000, published an excellent review of the chemomechanical means of caries removal. A promising new method of chemomechanical removal of dental caries is based on the principle of MID (Minimal intervention dentistry) and involves the application of chemicals.⁸⁵ Two chemicals, Carisolv and Caridex have been extensively evaluated and proven to be successful (Table 2.15). The principal mode of action is based on the use of sodium hypochlorite, a non specific proteolytic agent, and the effective interaction of 3-amino acids with carious dentin, removing organic components at room temperature. The gel is repeatedly applied to the carious dentin and softened caries is gently removed with specially designed hand instruments. These are scraping, non cutting instruments with 90° edges to facilitate the removal of softened dentin without removing the affected dentin (Figs 2.35A and B). This method causes less discomfort compared to drilling, but takes longer time (6 mins). The procedure did not require local anesthesia to the same extent and dentin caries was effectively removed without any adverse reactions.

The chemomechanical approach was initially introduced in 1972, in the form of the original GK-101 solution that contains N-monochloroglycine (NMG) and sodium hypochlorite. There were biochemical indications that GK-101 may disrupt the fibrillar organizations of collagen. In 1984, GK-101 E was introduced and marketed as Caridex, which contains N-monochloro D1, 2 aminobutyric acid (NMAB).

Carisolv is a relatively new material containing two solutions. The first contains glutamic acid, leucine, lysine, sodium chloride, erythrocin, CMC 200-800 cps, purified water and sodium hydroxide, with a pH of 11. The second solution contains sodium hypochlorite 0.5 percent.

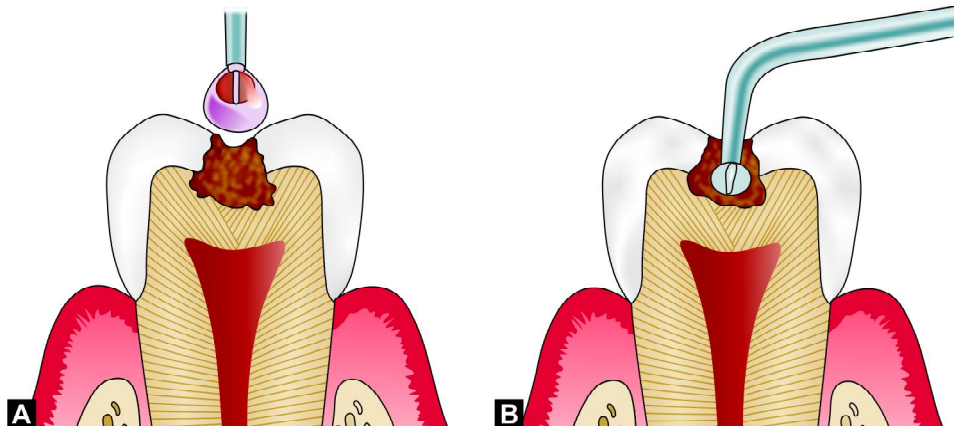
TABLE 2.15: Properties of two commonly available chemomechanical agents

	<i>Caridex</i>	<i>Carisolv</i>
Solution I	1% NaOCl	0.5% NaOCl
Solution II	0.1 M Amino butyric acid glycine 0.1 M NaOCl 0.1 NaOH	0.1 M Glutamic acid lycine NaOCl NaOH
Dye	—	0.2 Erythrocin (Pink)
pH	11	11
Consistency	Liquid	Gel
Volume needed	100-500 ml	0.2-1.0 ml
Time	5-15 mins	5-15 mins
Equipment	Applicator unit	None
Instruments	Tips	Specially designed

The active ingredient in Carisolv is sodium hypochlorite. When mixed with amino acids, it generates chloramines. This results in the chlorination of the partially degraded collagen, and the conversion of hydroxyproline to pyrrole-2-carboxylic acid, which initiates the disruption of collagen fibers and a selective softening of the outer layer of carious dentin. Due to the high pH, only the organic phase of dentin is affected. The high viscosity of Carisolv facilitates accurate placement and decreased volume of the material needed.⁸⁶

Lasers in Minimal Intervention Dentistry (Fig. 2.36)

Several early workers have described the potential of lasers in caries prevention. Lasers may increase caries resistance of enamel. Since the first description of their use in this field,



FIGURES 2.35A and B: Procedure for chemomechanical caries removal

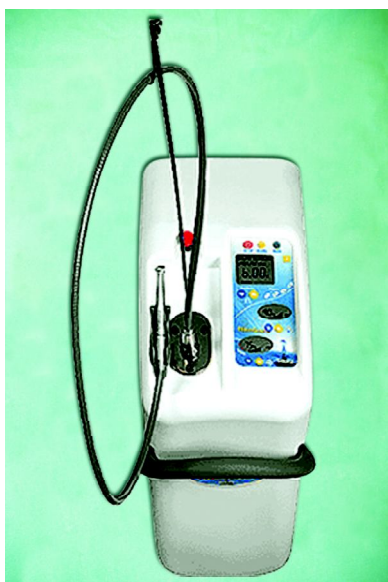


FIGURE 2.36: Lasers used for caries removal

nearly all the common laser wavelengths have been considered.⁸⁷

Nd:YAG lasers: Yamamoto suggested that caries could be prevented using Nd:YAG laser. Studies have shown that laser irradiation slightly alters the enamel surface, reducing subsequent subsurface demineralization. They have found a significant difference in solubility between laser-irradiated and non-irradiated enamel.

Hashimoto examined the effects of a continuous wave Nd:YAG laser on the acid resistance of defective rat enamel. He found that after irradiation, the defective enamel surface became smooth and small surface defects disappeared. The resistance to acid demineralization increased to match that of normal enamel.

CO₂ lasers: Florin has shown that a continuous wave CO₂ laser homogenizes the enamel surface by melting structural elements. The tissue in the laser-induced zones of fusion was harder than adjacent, non-irradiated enamel, which Florin suggested would increase the caries resistance.

Walsh reported the potential of the CO₂ laser for caries prevention using focused infra red laser radiation on sound enamel and early pit and fissure caries. Low power levels (2 to 5 W) induced localized melting and re-solidification of enamel with little surface destruction. For sound fissures, fusion of enamel on the lateral walls of the fissure eliminated the fissure space, providing a sealant effect. In carious fissures, carious enamel was vaporized and adjacent sound enamel fused to partially eliminate the defect. Walsh suggested that this technique had potential applications in sealing pits and fissures and producing physicochemical alterations in enamel, which might have preventive benefits.

The possible use of CO₂ laser treatment in the prevention of lesion progression in dental enamel has also been demonstrated.

Argon lasers: Argon lasers have been reported to reduce or prevent demineralization of enamel of extracted teeth using energy densities of 25 to 100 J/cm². At these energy densities, no damage would be expected in pulp or in the surrounding enamel. Argon irradiation of root surfaces significantly increases the resistance of cementum and underlying dentin to continual artificial caries attack. Lased cementum and dentin seem to have an increased affinity for uptake of fluoride, phosphorous and calcium ions and there is an apparently reduced lattice strain in hydroxyapatite following lasing.

These findings reported over many years, have established beyond doubt, the potential of lasers to enhance caries resistance. However, clinical trials which might establish the validity of the experimentally observed effects are lacking. This is almost entirely due to the lack of official approval for hard tissue applications.

Comparative investigations of the various wavelengths used are needed to determine the optimum operating regimens to maximize benefit and minimize side effects. The technique of X-ray microtomography might be of great value in this type of evaluation.

Er:YAG lasers: Dental enamel is the hardest tissue type in the body. Controlled cutting of enamel with lasers was an elusive goal for many years. Beginning with Stern and Sognnaes in 1964, different lasers have been tested for enamel ablation.⁸⁸ The final breakthrough came in 1997 in the United States with the FDA granting marketing clearance for the Erbium:YAG lasers. Initially, the clearances did not include children. By 1999, all three Er:YAG lasers were cleared for all ages.

The explosive interaction between the water molecules and the Er:YAG laser pulses on the tooth tissue surfaces disrupt enamel, dentin and decay. The action does not depend on heat. A constant spray of air and water is required. Cooling is present, although secondary to the provision of a water film on the surface for laser interaction. Some ablation of hydroxyapatite, the mineral of teeth, also occurs. Pulpal tolerance has been found to be better than with burs. The heat of friction with burs endangers the pulp as well as being the prime factor in patient discomfort. Almost all laser cavity preparations can be performed without anesthesia. Microfractures of enamel at the margins are not present with laser ablation.

Surface alteration, in addition to enamel removal, is achieved with Er:YAG lasers. The pulsing action creates a surface effect that resembles chemical etching with an expanded surface area and increased surface energy. Micro-retention in undercuts and punctuated surfaces aids bonding strengths. When acid and laser conditioning are combined, the bond strengths with restorative resins are greater than with either

method alone. Low power and pulse settings are the most appropriate for laser surface conditioning.

Cavity preparation is approached in a manner similar to conventional methods. Rubber dam is recommended for proper isolation. Topical anesthesia aids rubber dam clamp placement without requiring local anesthesia. The outline form is established at high energy settings for optimal cutting. On accessing dentin and decay, lowered energy parameters are used for decay removal and interior contouring. Even procedures near the pulp usually do not cause discomfort to the unanesthetized patient. No smear layer is formed and peritubular dentin may be cut more easily, opening tubules.

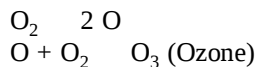
All types of cavity preparations can be performed with Er:YAG lasers (Class I, II, III, IV, V and VI). Crown preparations and removal of metallic restorations are contraindicated. Existing composite materials may be removed. Extraordinarily large and deep restorations may require anesthesia and may be prepared with bur and laser methods combined, with the bur used for enamel contouring and the laser for decay removal and surface conditioning.

Use of Lasers in Pit and Fissure Caries

Pit and fissure caries are ideal for laser treatment. Pit and fissure caries typically involve the organic part within an enamel defect. This plug material consists of food debris, bacteria, and remnants of the enamel-forming ameloblasts. Even though, there is no absorption of the laser in the enamel, the staining of the organic plug makes the material susceptible to the action of Nd:YAG lasers. The FDA has granted clearance for an Nd:YAG laser to be used to detect and remove the caries associated with pit and fissure lesions. The laser energy gives visual and acoustic response if organic plug material and caries are present. Otherwise, there is no interaction with the enamel. The approach works well with sealant placement. More extensive caries can be restored with the assistance of bur preparation. The pulsing action of the Nd:YAG laser has been found to reduce tooth sensitivity, reducing the need for anesthesia.

Use of Ozone in Minimally Intervention Dentistry

Ozone is a strong naturally occurring oxidizing agent in nature. It is produced by the action of UV rays on lightning in the atmosphere.



The first ozone generators were developed by Werner von Siemens in Germany in 1857. In 1870, the first report on ozone being used therapeutically to purify blood was given by C. Lender in Germany.⁸⁸ In 1885, the Florida Medical Association published "Ozone" by Dr. Charles J. Kenworth, MD, detailing the use of ozone for therapeutic purposes. In 1896, the electrical

genius Nikola Tesla patented his first ozone generator and in 1900, he formed the Tesla Ozone Company. In 1898, the Institute for Oxygen Therapy was started in Berlin by Thauerkauf and Luth. In 1913, the Eastern Association for Oxygen Therapy was formed by Dr. Blass and some German associates. During World War I, Ozone was used to treat wounds, trench foot, gangrene and the effects of poison gas. Dr. Albert Wolff of Berlin also used ozone for colon cancer, cervical cancer and decubitus ulcers in 1915.

In 1920, Dr. Charles Neiswanger, MD and the President of the Chicago Hospital College of Medicine, published "Electro Therapeutical Practice" that entitled "Ozone as a Therapeutic Agent".

Ozone kills more than 99 percent of all bacteria, fungi and viruses as this powerful oxidant readily penetrates through decayed tissue. Application of ozone to carious tooth surface produces a clean and sterile lesion that will remineralize easily and eliminate the need for placing restoration. FDA approves the use of ozone in the medical field.

Uses

- Dental cavity disinfections
- Root canal disinfections
- Oral candidiasis treatment
- Herpetic treatment
- Treatment of aphthous ulcer
- Stomatitis treatment
- Cleft lip and palate therapy

Contraindications: In the following cases, the ozone unit should not be used or be used with caution.

- Patients using cardiac stimulators (pacemakers).
- Epileptic patients or those suffering from other serious neurological illnesses.
- Patients suffering from psychological problems.
- On mucous membrane of infants (under one year old).
- Patients who are overly sensitive to electric currents.
- Patients suffering from serious asthma.
- Pregnant women.

Advantages

- Good efficacy in disinfection, killing bacteria and healing wounds.
- High concentration but low volume ozone precisely generated in the focused area.
- Disinfection effect of ozone lasts long.
- Eliminates worry of misuse of antibiotics.

Constitution

- A : Control Box
- B : Ozone Generating Handpiece
- C : Safety Rod (Ground Wire)
- D : Foot Pedal Switch

E : Power Adapter

F : Probe

Probes

No. 1 Probe: Pointed probe 10

For treatments of gingivitis

No. 2 Probe: Pointed probe 50

For treatments of gingivitis

No. 3 Probe: Flat probe

For treatments of skin and mucous membrane

No. 4 Probe: Conical probe

For alveolar therapies after tooth extraction

No. 5 Probe: Pointed probe 10 with conical plastic

For root canal treatments

Types of ozone generators: Ozone is the only gas that will pick up and hold electrical energy. In doing so, it becomes tremendously active and seeks to combine with all other substances. The list of substances that are inert to ozone is very short, and includes glass, Teflon, Kevlar, silicone and gold. Therefore, any ozone generator and auxiliary equipment must be composed of these substances only. There are several different techniques used to produce medical grade ozone, where freedom from contamination is critical. One type of generator uses an ultraviolet lamp as its source. It produces a very small amount of ozone in a narrow frequency bandwidth of ultraviolet light. Outside of the bandwidth, UV destroys ozone. An ultraviolet lamp is unreliable because it is subject to degradation over time, causing uncertainty regarding concentration and eventually burns out.

The second method of ozone production is corona discharge, where a tube with a hot cathode is surrounded by a screen anode. The best ones are called dual-dielectric, because they have a layer of glass separating each component from the gas stream. This prevents contamination of the ozone in the best designs, but heat is produced and heat destroys ozone. To compensate for the loss in concentration, more electricity is used, resulting in more heat and consequent electrical failure. This produces generators that have short lives. Lack of durability has always beset the ozone generator industry and was one of the major reasons for naturopaths mostly abandoning ozone therapy during the Thirties.

A third method of producing clean, medical grade ozone is called cold plasma. It uses glass rods filled with a noble gas and an electrostatic plasma field which turns the oxygen into ozone. Since there is no appreciable current, no heat is produced. Thus the generator will last a very long time, limited only by the quality of the power supply. The original cold plasma ozone generators were invented by Nikola Tesla in the 1920's and they still work 75 years later.

In ozone treatment, the tooth surfaces (pit and fissure) are cleaned with slurry of sodium bicarbonate and water (Prophy-

flex system) to remove stain and debris. DIAGNOdent is used to measure the occlusal areas for fluorescence of bacteria and indirectly the density of tooth structure and presence of decay. A number of units are commercially available that may be used for dental applications, e.g. *HealOzone*.

A burst of ozone gas at a preset concentration is delivered, after which the unit vacuums any residual ozone back through a catalyst that converts this ozone back to oxygen within another ten seconds. To complete the treatment, the HealOzone pumps a reductant fluid/mineral wash on to the treated site, to kick-start the remineralization process, which takes five seconds. So in just 25 seconds, elimination of microflora is achieved and healing starts, thus naturally restoring the tooth tissues. Seal must be achieved around the tooth surface to prevent the escape of the ozone, and without this seal the HealOzone will not produce ozone gas. An attractive home care kit, consisting of fluoride dentifrice, a bottle of mouth rinse and patient information booklet is provided for every patient to encourage remineralization and reversal of carious process. It is very critical to follow up the patient for 3 to 6 months and remeasure caries activity with DIAGNOdent.

Ozone concentration

Medical ozone is produced in varying concentrations. The quantity of ozone in comparison with the quantity of oxygen in the gas stream is called percent concentration. It is measured in micrograms of ozone per millimeter (or cc) of the mixture. A liter of oxygen weighs 1.4 grams.

$$0.5 \text{ percent} \times 1.4 \text{ gm} = 7 \text{ g/cc}$$

$$1.0\% \times 1.4 \text{ gm} = 14 \text{ g/cc}$$

$$1.5\% \times 1.4 \text{ gm} = 21 \text{ g/cc}$$

5 percent or 70 g/cc is considered to be the upper limit of concentration for internal use of medical ozone. Dr. Greenberg has shown, *in vitro*, that at concentrations of 90 g/cc, there was crimping of red blood cells, which was definitely harmful. Experiments by F. Sweet et al have shown inhibition of growth in healthy cells at concentrations above 72 g/cc. If one stays below that level, there will be few problems.

Ozone also stimulates production of superoxide dismutase, catalase and glutathione peroxide, which are the enzymes in the cell wall, which protect the cell from free radical damage.

Ozonated water: Ozone can be dispersed in water at 0.5 to 2 ppm. Research has shown that water whose bond angle is 101 degree is 'dead' water bereft of life-giving energy. The highest energy obtainable in liquid water is a bond angle of 109.5 degrees, and this is attainable by ozonating water at 4°C. Ozonated water is not stable for very long, even at 4°C. The ozone breaks up into an atom of elementary oxygen and a molecule of oxygen on contact with a substrate. This confers it good antibacterial property, because of which it is recommended for use as an endodontic irrigant.

Atraumatic Restorative Treatment (ART)

ART is a procedure based on excavating soft decalcified tooth tissue using hand instruments and restoring the cavity with an adhesive filling material. Initially, ART was developed in Tanzania in mid 1980's and introduced in a dental clinic setting in Malawi some years later. It was then evaluated under field conditions in Thailand in 1991. This was done by Dr. Jo. Frencken. Formally, the ART technique was released to the world on 7th April 1994 (i.e. The World Health Day) (Shan Farhan).⁹⁰ This procedure was developed because millions of people in less industrialized countries and special groups like refugees and people living in deprived communities are able to obtain dental care.

Conservative Operative Techniques

Operative recommendations according to the new classification are as follows:

Size 0: The lesion represents an area of demineralization on any of the three surfaces and can be treated by usual preventive measures. While treating a new lesion, minimize the removal of tooth structure, thus maintaining the natural strength of the crown and keeping the load of the restoration.

Site 1–size 0:⁹¹ The lesion dictates the concept of the fissure seal, as discussed by Simonsen, 1989. Sealing a deep fissure before it becomes partially occluded by plaque and pellicle, and in advance of demineralization into dentin, has an acceptable clinical history (Feigal, 1998; Ekstrand and others, 1998). The earliest fissure sealants were unfilled or lightly filled resins, but recent research has shown that there are some doubts about the integrity of the acid-etch union between resin and enamel in these regions. It has been shown that a glass ionomer will successfully occlude such a fissure (Wilson and McLean, 1988). This is now being termed “fissure protection” to differentiate it from a “resin seal”.

Anatomy of enamel within a fissure differs from that of other surfaces in that it is covered with a layer of enamel rods that appear to run parallel with the surface rather than at right angles. When it is etched with orthophosphoric acid, it will not develop the usual pattern of porous enamel that allows penetration of the unfilled resin that is normally relied upon to provide the micromechanical attachment (Burrow, Burrow and Makinson, 2001). The presence of this type of enamel may well account for the loss of the resin seal in many cases. Neither a resin nor a glass ionomer will flow into a fissure beyond the point where the fissure narrows down to approximately 200 μ m in width. So, retention of both materials appears to be dependent on adhesion to enamel at the entrance of the fissure rather than mechanical interlocking into the complexities of the fissure. Recent work suggests that even though the enamel

rods lie in a different orientation, glass ionomer will still develop ion exchange adhesion and show acceptable longevity.

Site 1–size 1: As the fissure walls become demineralized, the dentin will become involved as well. Radiographs will not show this early lesion very clearly and laser detector and electrical impedance machines have limitations. In the presence of strong, fluoridated enamel, the occlusal surface entry to the lesion will remain limited, and bacteria-laden plaque can be forced down into a defective fissure. In these circumstances, dentin involvement can become advanced before symptoms are noted.

The fissure system is a complex series of pits and fissures; therefore, a carious defect will often be limited to a very restricted area, leaving the remaining fissure system sound and uninvolved. This means that only the carious defect needs to be instrumented. Minor apparent defects should be explored in a very conservative manner before sealing the fissure system.

Site 1–size 2: In this classification, the lesion will either have progressed to some degree or it may represent replacement of a failed Class I restoration. Same conservative principles as in site 1–size 1 are applied and there is no need to open up the remaining fissures any further. If there is any part of the fissure system that is in doubt, it can be explored very conservatively, but it is sufficient to seal the fissures and any carious process below will be arrested. It will progress no further until there is access to the usual nutrients required by the bacteria again (Mertz Fairhurst and others, 1992). If there is any marginal leakage, there will be further bacterial activity, which is very unlikely when using glass ionomer because of ionic adhesion and the presence of fluoride release. Instrumentation and restoration techniques for these lesions will be the same as for a Size 1 lesion. But the occlusal involvement will be more extensive and, if there is any doubt about the ability of the glass ionomer to withstand the occlusal load, it can be cut back conservatively and laminated with resin composite.

Glass ionomer is used for restoration of both Size 1 and Size 2 lesions in this category. The restoration is well supported by the remaining tooth structure and the ion exchange adhesion will ensure complete sealing of the remainder of the cavity. If there is any demineralized dentin remaining on the floor of the cavity, there will be no further carious activity and there is a potential for remineralization (Ngo and others, 2001). It is possible to use a resin composite for the restoration but that would also mean cleaning the floor down to sound, healthy dentin to develop an acid-etch union with fully mineralized tooth structure. This may mean removing dentin that could otherwise be remineralized and healed.

Site 2–size 0:⁹² Proximal lesions progress very slowly because that surface is not under masticatory load and is, to a degree, protected from traumatic damage (Pitts, 1983; Shwartz and others, 1984). In contrast to the occlusal fissure lesion, it may

take up to four years to penetrate the full thickness of the enamel and an additional four years to progress through the dentin to the pulp. It is necessary to identify Size 0 and Size 1 lesions before any intervention, because it should be possible to heal the lesion and it is only when cavitation is established that a surgical technique is required. It is essential to avoid the use of a probe to explore the proximal surface because this is the quickest way to actually damage the enamel and cause a cavity.

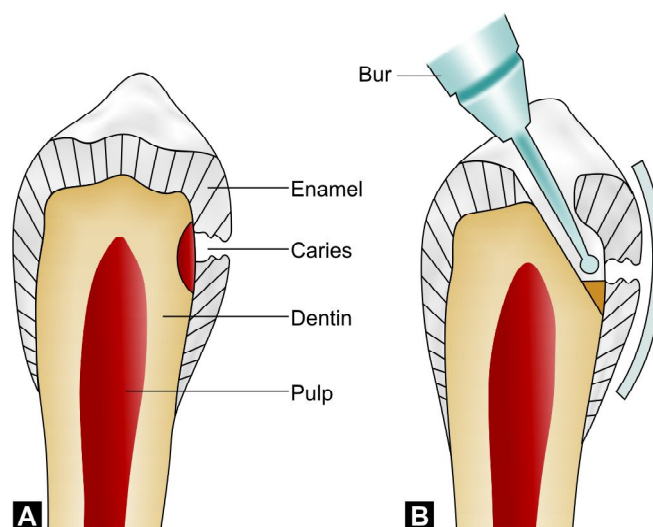
Site 2–size 1: In this case, cavitation is established on the proximal surface and surgical approach becomes essential. First, determine the position of the damage in relation to the crest of the marginal ridge. If it is more than 2.5 mm below the crest, then it may be possible to approach the lesion through the occlusal fossa and design a “tunnel” cavity (Hasselrot, 1998; Wilson and McLean, 1988). If it is less than this distance, a tunnel will only undermine the marginal ridge and weaken it still further. In this case, it is better to design a small box or “slot” cavity beginning on the outer slope of the ridge, retaining as much of the enamel as possible. Occasionally, a further alternative will present itself, when a large Site 2, size 3 or 4 lesion is being repaired or replaced and a small Size 1 lesion is revealed on the side of the adjacent tooth.

Site 2–size 1 “tunnel” (Figs 2.37A and B): Here, the contact area may remain sound and the marginal ridge may be quite strong, provided the lesion is more than 2.5 mm below the crest of the marginal ridge (Wilson and McLean 1988). Access to the lesion through the occlusal surface should be limited to the extent required to achieve visibility and, where possible, should be undertaken from an area that is not under direct occlusal load (Knight, 1984). For most patients, there is a fossa immediately medial to the marginal ridge that is the most suitable position for initial entry and, in a normal occlusion, is often not an area of occlusal contact. Resin composite is not indicated for restoration of these lesions because it will not be possible to access the proximal lesion to a sufficient degree to be able to reliably remove all demineralized enamel. It will not be possible to provide a beveled margin to ensure proper adaptation of the resin to the enamel. But glass ionomer will flow readily into a small cavity and has the ability to remineralize the enamel margins and any dentin on the axial wall that may be demineralized.

Tunnel preparations can be classified as:

1. Internal
2. Partial
3. Total

Internal tunnel preparation (or closed tunnel) is actually a class I cavity, which is appropriate when there are no macroscopically observable cavitations. The objective is to obtain remineralization of the enamel lesions.



FIGURES 2.37A and B: Tunnel cavity preparation for site 2–size 1 lesion

The **partial** tunnel preparation is indicated in the presence of macroscopically observable cavitations or when the enamel lesion disintegrates during cavity preparation. In such cases, the enamel may be carefully smoothed around the periphery of the opening, leaving the remaining part of the demineralized enamel to be remineralized.

In a **total** tunnel preparation, all demineralized enamel is removed.

The advantages of these preparations include:

- Preservation of tooth structure
- Maintenance of the marginal ridge and proximal contacts
- Avoidance of iatrogenic damage to the adjacent tooth during preparation
- Provision of fluoride supply to adjacent tooth tissue
- A small restorative perimeter and thereby reduced micro leakage

Instruments required

- Small, tapered diamond bur (#206) at intermediate high speed (40000 revs/min) with air/water spray, to open through the occlusal fossa.
- Small round burs, sizes 1/011 to 016, for caries removal.
- Long shank bur for difficult access.
- Access for hand instruments is limited, but the MC 1 double bladed chisels may be useful.

Site 2–size 1 “slot” (Fig. 2.38): A slot cavity could be used when the lesion is less than 2.5 mm below the crest of the marginal ridge and resin is the best material for this cavity design. Generally, the lesion will be obvious to visual examination, particularly when using magnification, because of the discoloration under the marginal ridge.



FIGURE 2.38: Slot cavity preparation for site 2—size 1 lesion

The outline form will be dictated entirely by the extent of the breakdown of the enamel, removing only that which is friable and easily eliminated without applying undue pressure. Remaining demineralized enamel will generally heal satisfactorily. Retention will again be through adhesion so it is only necessary to clean the walls around the full circumference of the lesion so there will be adhesion to the dentine as well. Leave the axial wall because it will consist of affected dentin only and will remineralize over a short period of time. Its removal will be a hazard to the pulp.

Instruments required

- Small, tapered diamond (#206) at intermediate high speed (40000 revs/min) with air/water spray, to open the outer slope of the marginal ridge.
- Small round burs, sizes 1/011-016, for caries removal.

Preparation and restoration: Use a small tapered diamond bur at intermediate high speed under air/water spray, and enter from the outer slope of the marginal ridge. Open buccally and lingually only as far as required to identify the cavitated enamel. Protect the adjacent tooth with a metal matrix band and leave this in place during restoration. Remove friable enamel rods carefully with a small hand instrument such as the MCI chisel. Retain a contact with the adjacent tooth wherever possible.

Use small round burs at slow speed to remove infected dentine from the full circumference of the lesion. Leave affected dentine undisturbed on the axial wall because it will remineralize and protect the pulp.

Condition the cavity and restore with the selected material. The most suitable material for the restoration will be a high-strength, auto-cure, radiopaque glass ionomer with the highest physical properties. A resin-modified material is satisfactory, provided it can be adequately light activated.

Place the glass-ionomer with a capsule or a disposable syringe to optimize adaptation to the cavity walls. Place

incrementally and use a small plastic sponge to tamp the cement to place. Use an occlusal matrix or a gloved finger, as a matrix to apply additional pressure.

Cut back the cement and laminate the occlusal entry with composite resin only if there is doubt about the ability of the cement to withstand the occlusal load.

Mini box restorations: This preparation was developed in order to treat caries lesions on proximal surface. Here, the marginal ridge is removed, which makes it different from tunnel preparations.

Site 2—Size 1—Proximal approach: A very conservative approach to restoring a proximal lesion can be achieved on limited occasions, such as when the proximal surface of a tooth becomes accessible at the time of cavity preparation in an adjacent tooth. The lesion may have been revealed through radiographs or may be noted only during cavity preparation.

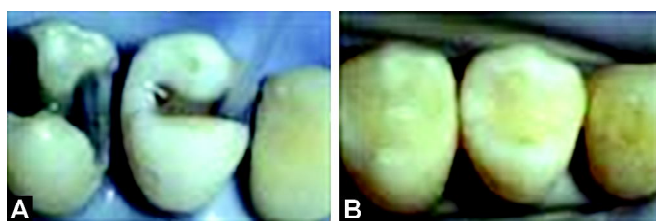
Instruments required

- Small, tapered diamond bur (#206) at intermediate high speed (40000 revs/min) with air/water spray, to open the enamel lesion.
- Small round burs, sizes 1/011-016, for caries removal.
- Use a long-shank bur for difficult removal.
- Access for hand instruments is limited, but the MC 1 double bladed chisel may be useful.

Preparation and restoration: Enlarge access into the enamel lesion using a small tapered diamond bur at intermediate high speed under air/water spray with good illumination and magnification. Remove the infected dentin with small round burs at slow speed. Burs with long shanks may be required for correct bur placement. Make sure the circumference of the cavity is completely clean to allow for the ion exchange adhesion to dentin. Leave affected dentin undisturbed on the axial wall because it will remineralize and protect the pulp.

Condition the cavity, and use a short length of a mylar or metal strip as a matrix, supported as required with a wedge. Restore using a high-strength, auto-cure radiopaque glass ionomer so that it can be monitored radiographically in future. Contour and polish immediately prior to placing the adjacent restoration.

Site 2—Size 2 and beyond (Figs 2.39A and B): These categories recognize the increasing size of the lesion and in many cases it will represent replacement dentistry where a failed GV Black Class II restoration has to be repaired or replaced. There will, of course, be neglected new lesions where there is a rather large proximal lesion and these should be dealt with keeping the same principles in MID. Often the occlusal fissure can be left uninvolved and possibly sealed as part of the restoration. Extension of the cavity margins will need to be sufficient to allow access to the lesion only to the extent that there will be



FIGURES 2.39A and B: Site 2–size 2 lesion restored with composite resin material

sufficient sound dentin exposed for proper adhesion around the full circumference. Unsupported enamel will be supported by the adhesive materials used for restoration and there is no need for extension to the so-called “caries free” areas.

When the lesion reaches these dimensions, it is likely that there will be a need to laminate the glass-ionomer base because the occlusal load will be beyond that, which can be safely handled over long term with the cement alone. This suggests that the lamination technique will be the method of choice.

Site 3–size 0: These lesions do not require restoration but they do need careful diagnosis and treatment planning to ensure they will no longer progress. All the potential causes have been discussed above, so effective treatment should not be difficult to achieve.

Site 3–size 1: A common lesion in this category will be the result of advancing erosion, abrasion or abfraction. It is important to both eliminate the cause and seal the lesion before it becomes too deep. Treatment should be kept very simple because a glass ionomer will adhere very effectively to the burnished sclerotic surface of the root through the ion exchange mechanism. This means that any form of cavity preparation, apart from conditioning, is strictly contraindicated because a smooth surface is the best for any form of chemical adhesion.

Instruments required: For the erosion of lesion, there will be no instruments required because the cavity need not be prepared at all.

For the small carious lesion, use a small round bur only to clean the walls sufficient to allow ion exchange adhesion.

Preparation and restoration: For the erosion lesion, clean lightly with slurry of pumice and water on a small rubber cup to remove any plaque on the surface of the lesion and ensure complete adaptation of the glass ionomers to the tooth. In the presence of active caries, clean the walls around the full circumference but leave the axial wall to remineralize under the glass ionomer.

Condition the surfaces of the cavity with 10 percent polyacrylic acid for 10 seconds only, wash well and dry lightly. Select a suitable matrix and pre-form as required. Mix the appropriate material. Syringe the glass ionomer on to the tooth surface and apply the matrix to adapt the material well and positively to the surface of the tooth.

Light activate or allow the glass ionomer to set. Check the excess around the periphery of the matrix to see that it is properly set. Remove the matrix and immediately apply a generous coating of a low viscosity resin as a sealant. This is essential only for the auto-cure material, but is still a good idea for the resin-modified material. Use a sharp blade to minimally trim an auto-cure material before light-activating the resin seal. Use fine diamonds under air/water spray to contour a resin-modified material and then seal it again with the low viscosity resin seal.

Polish the restorations after the glass ionomer has matured, only if it is essential. If the matrix was properly applied, subsequent polishing is often not required.

Site 3–size 2: These lesions will generally be cavities resulting from active caries. They will vary from the Size 1 lesion only in relation to their size and they will be more of a challenge to restore. The usual instrumentation will be required to remove the demineralized infected dentin on the surface before restoring. Clean the walls around the periphery only although, almost certainly, there will be affected dentin remaining on the floor of the cavity. However, as long as the margin is sealed against micro leakage, the restoration will be effective and the affected dentin will heal.

Instruments required

- For this larger carious lesion it may be necessary to extend the margins a little using a small tapered diamond bur (# 206)
- Use a small round bur to clean the walls sufficient to allow ion exchange adhesion.

The preparation is essentially the same as described for the site 3–size 1 lesion.

Site 3–size 3:⁹³ These lesions are generally root surface lesions on the interproximal surfaces of anterior or posterior teeth. Under these circumstances, it will often be prudent and conservative to enter the lesion from either the buccal or the lingual rather than from the occlusal. The decision concerning the side of entry will be dictated primarily by the position of the lesion and secondarily by the need for access and convenience. It is, of course, possible in a young patient, to approach an initial lesion that lies immediately under the contact area with this design. However, the closer the cavity is to the marginal ridge, the more likely it is that the ridge will fail at a later date. The lesion in the older patient will be beyond the cemento-enamel junction and therefore well below the contact area, so remaining tooth structure is less likely to fail subsequently.

Instruments required

- Small, tapered diamond bur (#206) at intermediate high speed (40,000 revs/min) under air/water spray.
- Small round burs, sizes 1/011-016, for caries removal.

- Long shank round burs may be required for deep access.
- Access for hand instruments is limited.

Preparation and restoration: Enter the lesion from the buccal or the lingual as the position of the carious lesion dictates, using the small tapered diamond stone at intermediate high speed under air/water spray. Use a short length of a metal matrix to protect the adjacent tooth while working. Wedge the matrix carefully, when placing the cement.

Begin slightly occlusal to the lesion, and move interproximally and gingivally until the lesion is clearly visible. Sacrifice sufficient tooth structure or old restoration to allow access and convenience form without unduly weakening the marginal ridge. Use small round burs at slow speed to remove all infected dentin and develop clean walls around the entire circumference. Leave the axial wall, even though it is demineralized. If possible, retain the wall at the opposite side from the entry to provide a positive finishing line for the restoration.

Restore using a radiopaque glass ionomer. If access is available for correct placement of the activator light, use a resin-modified material. Trim and contour carefully after placement to ensure there is no overhang or over-contour. Seal with a very low viscosity light-activated resin enamel seal.

Sandwich technique/dentin “replacement”: It is perhaps difficult to distinguish or delineate between using glass ionomers as liners, dentinal adhesives, and the sandwich technique. The sandwich technique gets its name from the fact that, in this particular usage, glass ionomers are “sandwiched” between the tooth surface below and the (other) restorative material above, usually being resin composite. There are a number of articles promoting the use of this technique, with more limited exposure to clinical testing of the technique with reported outcomes. The impressive 91 percent success rate of restorations in the primary dentition, reported by Mjor, indicated that 9 percent restoration failure group was represented by a 9 percent failure rate of amalgam restorations, 8 percent failure rate of traditional glass ionomer cement restorations and 7 percent failure rate of resin-modified glass ionomer cement restorations.⁹⁴

MANAGEMENT OF DEEP DENTAL CARIES IN CHILDREN

Introduction

- Treatment of pulpally inflamed primary and permanent teeth in children presents a unique challenge to the dental clinician because of consideration of a variety of factors such as stage of development of the tooth and anatomy of the tooth.
- Importance of preoperative diagnosis cannot be overemphasized as without a sound diagnosis, it is impossible to render adequate treatment for a diseased tooth.
- Pulp diagnosis in a child is often imprecise as clinical symptoms do not correlate well with histological pulpal status.
- The age and behavior compromise reliability of pain response in children.
- The most important and difficult aspect of pulp therapy is determining health status of pulp or degree of inflammation.
- Treatment goals are developmentally oriented in pediatric dentistry.

Need of Pulp Therapy in Children

- It is very high in developing countries due to a high caries severity index as also the high DMF/DMFT scores.
- Lack of awareness and lack of adequate preventive practices add to the high caries rate in developing countries.
- Dietary patterns, particularly a cariogenic diet also add to the above.
- Anatomy of primary teeth (thinner enamel layer, more porous dentinal tubules, marked cervical constriction) is a significant factor due to which spread of caries in deciduous teeth is more rapid and also affects their restorative treatment modality.

Objectives of Pulp Therapy in Children

“The successful treatment of a pulpally involved tooth is to retain that tooth in a healthy condition, so it may fulfill its role as a useful component of the primary and young permanent dentition.” (Lewis and Law)

Effects of Premature Loss of Primary Teeth

- Loss of arch length.
- Insufficient space for erupting permanent teeth.
- Ectopic eruption and impaction of premolars.
- Mesial tipping of molar teeth adjacent to primary molar loss.
- Extrusion of opposing permanent teeth.
- Shift of the midline with a possibility of crossbite.
- Development of certain abnormal tongue positions.

Effects of Caries on the Pulpodentinal Organ

- Carious process forms three different forms of irritants:
 1. Biologic irritants.
 2. Chemical irritants.
 3. Physicomechanical irritants.
- Considerable controversy exists about the depth of carious lesion and pulp status.
- M S Duggal⁹⁵ observed that the response of primary pulp to carious attack is poorly understood.
- Mortimer, 1970,⁹⁶ McDonald, 1994,⁹⁷ stated that the anatomy of primary teeth is different in the following ways:

- Smaller dimension.
- Thin, permeable, less calcified enamel.
- Permeable, thin dentin.
- Large pulp chambers and prominent horns.
- These studies revealed that inflammation of pulp in primary molars develops at an early stage of proximal caries.
- Hence, large proximal restorations in primary teeth without due consideration to the pulp are doomed to failure.
- These diverse results merely confirm that many factors are involved in the type of reaction of the pulpodental organ towards caries.

Specific Treatment Modalities

Following factors should be considered before deciding upon a specific treatment modality:

Type of Decay

- More acute caries, less effective reparative mechanism. Chronic decay is usually accompanied by substantial repair, provided caries has not extended to the pulp.
- If chronic decay involves pulp, then a destructive reaction should be expected.

Duration of Decay Process

- Longer duration of acute decay leads to more massive destruction of tooth structure.
- Longer duration of chronic decay leads to more time for repair if pulp is not involved.

Depth of Involvement

- Deeper the caries is, nearer are the sources of irritation to the pulp with greater possibility of pulpal destruction.
- May be classified into:
 - Peripheral Involvement.
 - Moderate Involvement.
 - Profound Involvement.
 - Perforating Involvement.

Number and Pathogenicity of Microorganisms

- Greater the virulence and population of microorganisms, greater is the likelihood of pulpal reaction.
- Number of virulent microorganisms found in a caries inactive mouth is considerably higher than that in a caries active mouth.

Tooth Resistance

- Thickness of dentin.
- Permeability of dentin.
- Fluoride and calcium content of involved dentin.
- Susceptibility of tooth—all these factors affect the resistance of a tooth to the caries attack.

Concept of “Effective Depth”

- It is the area of minimum thickness of sound dentin separating the pulpal tissues from carious lesions.

Sr. No.	Infected Dentin	Affected Dentin
1.	Bacterial invasion	No bacterial invasion
2.	Distorted tubules	Intact tubules
3.	Degeneration of odontoblastic process	Intact odontoblastic process
4.	Not capable of remineralization	Capable of remineralization if pulp is vital

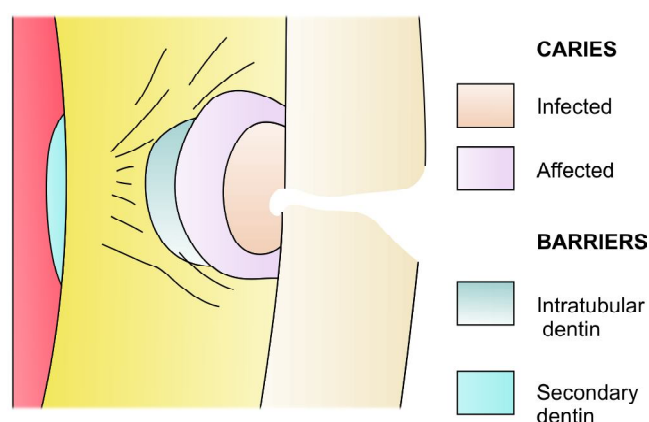


FIGURE 2.40: Infected and affected dentin

- It is usually found in the deepest portion of the carious cavity.
- Effective Depth = 2 mm or more: healthy reparative reaction.
- Effective Depth = 0.8 to 2 mm: unhealthy pulpal reaction.
- Effective Depth = 0.3 to 0.8 mm: moderate to severe pulp reaction.

Concept of “affected” and “infected” dentin (Table 2.16 and Fig. 2.40)

- Bacteria never penetrate as far as the advancing front of the lesion.
- Infected dentin is softened and contaminated with bacteria.
- Affected dentin is softened dentin but not yet invaded by bacteria.

Incidents of macroscopic direct pulp exposure

- Whenever a carious lesion extends 3 to 4 mm pulpally or axially to DEJ, visible perforation to the pulp chamber can be expected in 75 percent cases.
- In younger tooth, the probability of perforation increases.
- Perforation incidents increase, as the lesion occurs more apically on the axial wall.

TABLE 2.17: Relation of pulp exposure with the degree of pulp inflammation

Exposure size	Peripheral dentin	Bleeding	Status of pulp inflammation	Repair ability of pulp
Pin-point	Sound	Absent	Absent	Excellent
Pin-point	Sound	Very mild and coagulative	Mild	Good
>0.5 mm	Carious	Absent	Moderate	Borderline
>0.5 mm	Carious	Profuse	Moderate/severe	Absent
>0.5 mm	Soft carious	Profuse with pus	Severe	Absent

Incidents of microscopic direct pulp exposure:

- Peripheral pulp tissue is relatively avascular.
- Blood vessels are very narrow and tortuous which impedes the passage of RBC, WBC.
- Hence, if these layers are involved in excavating carious dentin, there will be no hemorrhage observed from perforation.
- Only evidence of an exposure is oozing of colorless dental pulp fluid which can be detected microscopically.

What is a pulp exposure? (Table 2.17)

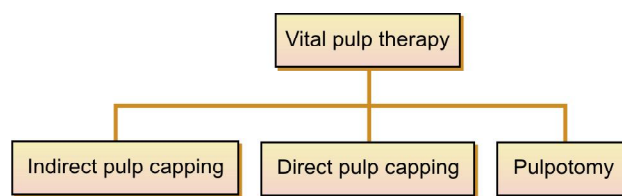
- An exposure of dental pulp exists when the continuity of the dentin surrounding the pulp is broken by physical or bacterial means.
- It is usually accompanied by symptoms which are most indicative of the actual condition of pulpodentinal organ.
- It gives an idea about the repair abilities of the dental pulp.
- Lower the ratio of exposure diameter relative to the dimensions of pulp and root canal, greater will be the possibility of repair and healing of the pulpodentinal organ.
- Closer the exposure to anatomical constrictions in pulpal chamber, lesser will be the repair possibilities.

PULP TREATMENT PROCEDURES

- They can be classified as:
 - Vital pulp therapy (Fig. 2.41).
 - Non-vital pulp therapy.
- They can be also classified as:
 - Conservative pulp treatment.
 - Radical pulp treatment.

Vital Pulp Therapy

Refer Fig. 2.41

**FIGURE 2.41: Schematic representation of vital pulp therapy procedures****Indirect Pulp Capping**

Indirect pulp capping is defined as the application of a medicament over a thin layer of remaining carious dentin, after deep excavation, with no exposure of the pulp.

Indirect pulp capping may be defined as the removal of the infected layer of dentin and the placement of a medicament against the noninfected dentin in order to remineralize the underlying demineralized tissue.⁹⁸

Objectives

- To avoid pulp exposure.
- To avoid need of more invasive pulp therapy.

Historical review

- Indirect pulp capping was first described by Pierre Fauchard in the 18th century.
- John Tomes in the 19th century put forth the idea of leaving discolored dentin to avoid sacrifice of a carious tooth.
- WD Miller put forth the concept of sterilization of dentin.
- GV Black, however, refused to accept the idea of leaving behind caries in a tooth irrespective of pulpal exposure.

Rationale

Decalcification of dentin precedes bacterial invasion within dentin, hence the removal of dentin infected with bacteria may provide a suitable environment for the remineralization of the decalcified dentin.

Difference between outer and inner carious dentinal layers?

- Outer layer of carious dentin:
 - Irreversibly denatured
 - Infected
 - Incapable of being remineralized
- Inner layer of carious dentin:
 - Reversibly denatured
 - Not infected
 - Capable of being remineralized

Evidence based conclusions

- Cultures of deep layers of remaining carious lesions are nearly always infected with microorganisms before treatment.
- Cultures of successive layers of carious dentin have uninfected demineralized dentin below it.

- If only a few bacteria remain in the dentin and find their way to the pulp, they will be inactivated by healthy pulp.
- However, Whitehead et al stated that only 51 percent samples were free from signs of organisms after complete removal of soft dentin.⁹⁹
- Shovelton observed that primary teeth showed more bacteria after removal of carious dentin.¹⁰⁰
- The above observation was supported by Seltzer and Bender.¹⁰¹
- Thus, complete clinical removal of carious dentin does not necessarily ensure that all infected tubules have been eradicated.

Studies about the coping ability of pulp for minute contaminations

- Reeves-Stanley¹⁰² and Shovelton¹⁰³ found that when caries is 0.8 mm away from the pulp; no significant inflammatory changes occur in permanent teeth.
- Rayner and Southam¹⁰⁴ observed that in primary teeth this distance ranges from 0.6-1.5 mm for inflammatory changes to occur.

Indirect pulp capping

Indications

Case selection should be based upon following findings:

History

- Mild discomfort from chemical and thermal stimuli
- Absence of spontaneous pain

Clinical examination

- Large carious lesion
- Absence of lymphadenopathy
- Normal appearance of adjacent gingiva
- Normal color of tooth

Radiographic examination

- Large carious lesion in close proximity to the pulp
- Normal lamina dura
- Normal periodontal ligament space
- No interradiolar or periapical radiolucency

Contraindications

History

- Sharp, penetrating pain that persists after withdrawal of stimulus
- Prolonged spontaneous pain, particularly at night

Clinical examination

- Excessive tooth mobility
- Parulis in the gingiva approximating the roots of the tooth
- Tooth discoloration
- No response to pulp testing techniques

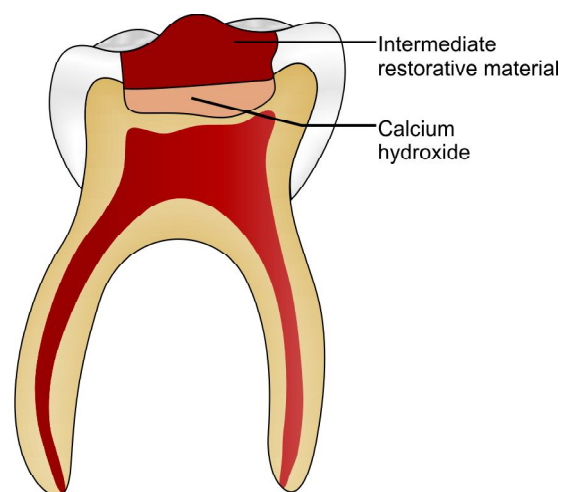


FIGURE 2.42: Placement of calcium hydroxide in indirect pulp capping

Radiographic examination

- Large carious lesion with apparent pulp exposure
- Interrupted or broken lamina dura
- Widened periodontal ligament space
- Radiolucency at the root apices or furcation areas

Two sitting procedure of indirect pulp capping

- Anesthetize the tooth and apply the rubber dam.
- Establish the outline form.
- Remove the soft, necrotic, infected dentin with a large round bur at slow speed.
- Remove the peripheral dentin with a spoon excavator.
- Cover the remaining affected dentin with hard set calcium hydroxide (Dycal, Reocap, Renew) (Fig. 2.42).
- Fill the cavity with intermediate restorative material (IRM).
- Obtain a bitewing radiograph (Fig. 2.42).

Second Visit (six to eight weeks later):

- Ask history of pain, obtain a radiograph.
- Anesthetize the tooth and apply the rubber dam.
- Remove all temporary restorative material including calcium hydroxide with caution.
- Observe the affected dentin; it should be dry, flaky and easily removable.
- Observe the area of potential exposure; it should be white and may be soft.
- Do not disturb this predentin.
- Irrigate with normal saline and dry with cotton pellets.
- Cover the entire floor with hard set calcium hydroxide
- Place a suitable base and restore with a permanent restorative material.

One-sitting procedure

- Value of re-entry and re-excitation is questionable.
- There is a potential risk of pulp exposure due to overzealous excavation.
- Leung et al¹⁰⁵ and Fairborne et al¹⁰⁶ observed that re-entry is not necessary as long as the tooth is asymptomatic and a good seal is maintained.

Clinical and radiographic criteria of success

- Restoration is intact.
- Tooth has no mobility.
- No sensitivity to percussion.
- No history of pain after treatment.
- No radiographic evidence of abnormal root resorption.
- No radiographic evidence of radicular disease.

Histological Evaluation

- Given by **Law and Lewis**¹⁰⁷
 1. Irritational dentin formation.
 2. Intact zone of Weil.
 3. Slight hyperactive pulp with inflammatory cells.

Conclusion

From these reports (Table 2.18), it appeared that gross caries removal, together with a palliative dressing and proper sealing of the cavity, will arrest the carious process by eliminating substrate and bacterial action.

Direct Pulp Capping

- **Fuks AB:** Direct pulp capping involves the placement of a biocompatible agent on healthy pulp tissue that has been inadvertently exposed by caries excavation or a traumatic injury.¹⁰⁸
- Direct pulp capping may be defined as the treatment of an exposure of the dental pulp caused by an accident or in the course of excavating deep caries. It is generally recom-

mended when a mechanical exposure occurs in a dry sterile field.⁹⁸

Objectives

- To seal the pulp against bacterial leakage, encourage the pulp to wall off the exposure site by initiating dentin bridge formation.
- To maintain vitality of the pulp.

Indications

- No signs or symptoms of degeneration of the pulpodentinal organ.
- Field of operation should be completely aseptic.
- Exposure should be
 - Pin-point size.
 - No observable hemorrhage.
 - Dentin at the periphery of the exposure should be repairable and sound.
 - Exposure site should not be at a constricted area in the pulp.

Procedure of direct pulp capping

- Anesthetize the tooth and apply the rubber dam.
- Establish the outline form.
- Remove caries and make a conventional cavity preparation (which has resulted in a pinpoint exposure).
- Gently clean the preparation with H₂O₂ (not recommended by many investigators).
- Evaluate quality of hemorrhage and make sure bleeding stops quickly.
- Place Calcium Hydroxide (Dycal) directly on exposure.
- Place appropriate base and final restoration.

Clinical success is determined by:

- Maintenance of pulp vitality.
- Absence of pain.
- Absence of abnormal radiographic signs
- Dentin bridge formation.

Jeppesen, in a long-term study using a creamy mix of calcium hydroxide, placed on exposed pulps of primary teeth, reported a 97.6 percent clinical success and 88.4 percent histologic success.¹⁰⁹

Are primary teeth good candidates for direct pulp capping?

- DPC in primary teeth has been viewed with skepticism.
- The following are the limitations of direct pulp capping in primary teeth:
 - Internal resorption.
 - Calcification.
 - Chronic pulp inflammation.
 - Necrosis.
 - Interradicular involvement.

TABLE 2.18: Success rate of indirect pulp capping

Sr. No.	Investigators	Cases	Period	Success %
1.	Sowden, 1956	4,000	Up to 7 yr	"Very high"
2.	Hawes and DiMaggio, 1964	475	Up to 4 yr	97
3.	Jordan and Suzuki, 1971	243	10-12 wk	98
4.	Nordstrom et al 1974	64	94 days	84
5.	Nirschl and Avery, 1983	83	6 months	94

CALCIUM HYDROXIDE

Calcium hydroxide Table 2.19.

TABLE 2.19: Antibacterial effect of setting calcium hydroxide paste materials

Sr. No.	Strong effect	Medium effect	No effect
1.	Dycal (Original formula)	Dycal (New formula)	MPC Kerr, Romulus, Michigan, USA
2.	Reocap Vivadent, Schaan/Liechtenstein	Life Kerr, Romulus, Michigan, USA	Hydrex
3.	Procal	Renew SS White Co./Dentomax, Bradford, UK	Cal- Mer Experimental cement devised by Laboratory of Government Chemist, Cornwall house, Stanford St, London, UK
4.		Reolit Vivadent, Schaan/Liechtenstein	

Non-setting Calcium Hydroxide (Table 2.20)

TABLE 2.20: Various non-setting calcium hydroxide materials used

Material	Vehicle
Analar $\text{Ca}(\text{OH})_2$	Water
Pulpdent (Pulpdent Corp. of America)	Methyl cellulose
Hypo-Cal (Ellman Dental Manufacturing Co. Int., USA)	Methyl cellulose
Reogan	Methyl cellulose

Role of Calcium Hydroxide (Fig. 2.43)

Some investigators have proposed that $\text{Ca}(\text{OH})_2$ stimulates undifferentiated mesenchymal cells to differentiate into cementoblasts, which in turn initiate cementogenesis at the apex. Dylewski observed proliferating connective tissue in the apical region that differentiated into calcific material, which became continuous with the predentin at the apex.¹¹⁰ Schroder and Granath mentioned that this calcification process occurs beneath a superficial layer of necrosis.¹¹¹ They considered that the necrosis was related to the pH of the $\text{Ca}(\text{OH})_2$.

Heithersay considered that alkalinity of the material can act as a buffer to acidic inflammatory reactions.¹¹² As a result, the $\text{Ca}(\text{OH})_2$ has a favorable effect on bone healing. Tronstad

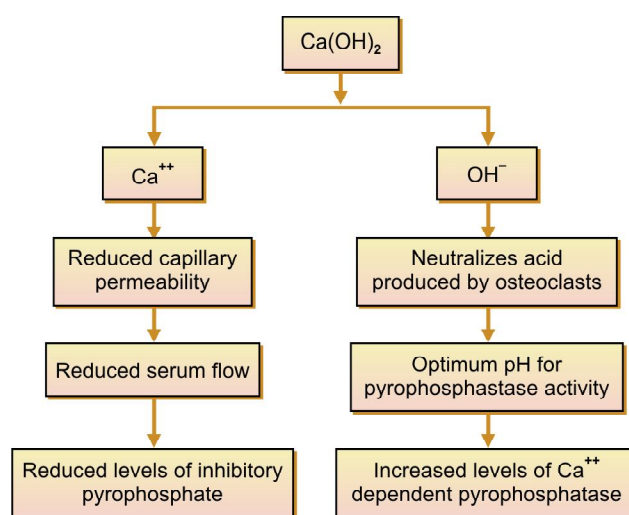


FIGURE 2.43: Schematic representation of mechanism of action of $\text{Ca}(\text{OH})_2$ cement

and coworkers have shown that the pH of untreated teeth with pulpal necrosis lies between 6.0 and 7.4.¹¹³ Teeth with complete root formation have a pH between 7.4 and 9.6 in the dentin away from the pulp and from 8.0 to 11.1 in the dentin next to the pulp. These investigators mentioned that the $\text{Ca}(\text{OH})_2$ neutralizes the acids produced by osteoclasts. Anthony and coworkers concluded that the alkaline environment would favor the formation of calcium-phosphate $[\text{Ca}(\text{PO}_4)]$ complexes, which would in turn; serve as a nidus for further calcification.¹¹⁴ Javelet and coworkers also indicated that the alkalinity is a significant feature in the ability of $\text{Ca}(\text{OH})_2$ to induce hard tissue formation.¹¹⁵ Other investigators contended that $\text{Ca}(\text{OH})_2$ creates an unfavorable environment for osteoclastic activity or can activate alkaline phosphatase enzymes. The latter have been suggested as playing a role in hard tissue formation. It has been shown that $\text{Ca}(\text{OH})_2$ by itself and as a component of root canal sealers can induce calcification even in a soft tissue environment.

When preparing the $\text{Ca}(\text{OH})_2$ paste using anesthetic solutions, Stamos and coworkers determined that such a small amount of liquid is used that no appreciable change occurs in the pH.¹¹⁶ Mitchell and Shankwalker concluded that it is difficult to ascribe any importance to the pH of the material when the osteogenic potential is considered.¹¹⁷ They rationalized that the use of other materials that have relatively high pH values do not result in consistent hard tissue formation.

Mc Cormick and coworkers¹¹⁸ mentioned that the reliance on medication alone to accomplish a pH rise in the periapex as proposed by Van Hassell and Natkin,¹¹⁹ is unrealistic. They believed that the other procedures are of considerable importance in gaining continued apical development. These procedures include:

- Adequate preparation of the root canal
- Removal of necrotic tissue and substrate
- Reduction of microbes (both in terms of numbers and virulence)
- A decrease in root canal space.

Frank concluded that the reduction of contaminants in the root canal and filling of the root canal space with a temporary resorbable material are more important than which material is used.¹²⁰

Nyborg and other investigators thought that pulpal reactions to Ca(OH)_2 depended on the hydroxyl ion rather than the calcium ion.¹²¹ Nevertheless, in one study, in which magnesium hydroxide was used in fourteen apexification procedures, the results showed four mild and ten severe inflammatory reactions. Contradictory results were found when magnesium hydroxide was implanted subdermally in rats. Magnesium hydroxide was found to have less of an inflammatory reaction than has Ca(OH)_2 . In one investigation, barium hydroxide was substituted for Ca(OH)_2 . Observations from this study included a lack of bridge formation, a severe foreign body reaction, and an acute and chronic inflammation with epithelial proliferation.

The calcium ion was also thought to be necessary to decrease capillary leakage and constrict the pre-capillary sphincters. In addition, the calcium ion can also affect the enzyme pyrophosphatase, which is calcium dependent. Pyrophosphate is involved in collagen synthesis and therefore stimulation of this enzyme can increase the defense and repair mechanism.

Nevins and coworkers used $\text{Ca(PO}_4\text{)}$ gel to produce mineralized scar around the orifices of polyethylene tubes that were placed subcutaneously in the rats.¹²² When placed in pulp-less open apex teeth in monkeys, the gel resulted in connective tissue ingrowth. Nevins et al¹²² postulated that this could be a step in revitalization of the teeth. In other studies, the Nevins group also reported the successful use of collagen $\text{Ca(PO}_4\text{)}$ gel. In contrast Citrome and coworkers found that in dogs the collagen $\text{Ca(PO}_4\text{)}$ gel inhibited the reparative process of the initial inflammatory lesion, leading to extensive destruction of the periapical tissues.¹²³ No evidence of apexification was found. They also reported that collagen $\text{Ca(PO}_4\text{)}$ also failed to assist in resolution of instrumentation trauma and inhibited the repair process. Teeth treated with Ca(OH)_2 in the same animals showed an acceleration of the repair process.

Finally, whether or not a complete apical barrier results from apexification techniques is uncertain. **Lieberman and Trowbridge** have shown that even with radiographic and clinical evidence of a hard tissue barrier, histologic examination shows that this barrier is porous.¹²⁴ Nevertheless, for clinical success, it may not be necessary to have an impermeable hard tissue barrier.

Alternative Agents to Calcium Hydroxide Suggested for Direct Pulp Capping in Primary and Permanent Teeth

Zinc Oxide–Eugenol cement: **Glass and Zander** found that ZOE, in direct contact with the pulp tissue, produced chronic inflammation, a lack of calcific barrier, and an end result of necrosis.¹²⁵ In spite of the reported lack of success with ZOE cement, Sveen reported 87 percent success with the capping of primary teeth with ZOE in ideal situations of pulp exposure.¹²⁶

Corticosteroids and antibiotics: Corticosteroids and/or antibiotics were suggested for direct pulp capping in the pretreatment phase and also to be mixed in with calcium hydroxide with the thought of reducing or preventing pulp inflammation. These agents included neomycin and hydrocortisone,¹²⁷ Cleocin,¹²⁸ cortisone,¹²⁹ Ledermix (calcium hydroxide plus prednisolone),¹³⁰ penicillin,¹³¹ and Keflin (cephalothin sodium).¹³² Although many of these combinations reduced pain for the most part, they were found only to **preserve chronic inflammation** and/or reduce reparative dentin. Gardner et al found, however, that vancomycin, in combination with calcium hydroxide, was somewhat more effective than calcium hydroxide used alone and stimulated a more regular reparative dentin bridge.¹³³

Polycarboxylate cements: **Negm et al** placed calcium hydroxide and zinc oxide into a 42 percent aqueous polyacrylic acid and used this combination for direct pulp exposure in patients from 10 to 45 years of age. This mixture showed faster dentin bridging over the exposures in 88 to 91 percent of the patients when compared to Dycal as the control.¹³⁴

Inert materials: Inert materials such as isobutyl cyanoacrylate¹³⁵ and tricalcium phosphate ceramic¹³⁶ have also been investigated as direct pulp-capping materials. Although pulpal responses in the form of reduced inflammation and unpredictable dentin bridging were found, to date, none of these materials have been promoted to the dental profession as a viable technique.

Collagen fibers: Because collagen fibers are known to influence mineralization, **Dick and Carmichael** placed modified wet collagen sponges with reduced antigenicity in pulp-exposed teeth of young dogs.¹³⁷ Although, the material was found to be relatively less irritating than calcium hydroxide, and with minimal dentin bridging in eight weeks, it was concluded that collagen was not as effective in promoting a dentin bridge as was calcium hydroxide.

Formocresol: Because of the clinical success of formocresol when used in primary pulp therapy such as pulpotomies and pulpectomies, several investigators have been intrigued by the possibility of its use as a medicament in direct pulp-capping

therapy. **Arnold** applied full-strength formocresol for 2 minutes over enlarged pulp exposures in primary teeth and found a 97% clinical “success” after 6 months.¹³⁸

Hybridizing bonding agents: Recent evidence has shown that elimination of bacterial microleakage is the most significant factor affecting restorative material biocompatibility.¹³⁹ Currently, hybridizing dentinal bonding agents (such as AmalgamBond or C and B MetaBond, Parkell Products, Farmingdale, N.Y.) represent the state of the art in mechanical adhesion to dentin with resultant microleakage control beneath restorations.¹⁴⁰ Miyakoshi et al have shown the effectiveness of 4-META-MMA-TBB adhesives in obtaining an effective biologic seal.¹⁴¹ Cox et al demonstrated that pulps sealed with 4-META “showed reparative dentin deposition without subjacent pulp pathosis.”¹⁴²

Cell-inductive agents: A number of cell-inductive agents have been proposed as potential direct pulp-capping alternatives to calcium hydroxide. These contemporary substances mimic the reciprocal inductive activities seen in embryologic development and tissue healing that are receiving so much attention at this time.

- **Mineral trioxide aggregate (MTA) (Dentsply, Tulsa; Tulsa, Okla):** MTA was developed at Loma Linda by Torabinejad for the purposes of root-end filling and furcation perforation repair.¹⁴³ The material consists of tricalcium silicate, tricalcium aluminate, tricalcium oxide, and silicate oxide. It is a hydrophilic material that has a 3-hour setting time in the presence of moisture. Major MTA advantages include excellent sealing ability, good compressive strength (70 MPa) comparable to IRM, and good biocompatibility. Pitt Ford et al documented superior bridge formation and preservation of pulp vitality with MTA when compared with calcium hydroxide in a direct pulp-capping technique.¹⁴³ They also reported normal cytokine activity in bone and cementum regeneration in response to MTA, which is indicative of its cell-inductive potential.¹⁴⁴
- **Calcium phosphate cement:** It has been developed for repairing cranial defects following brain neurosurgery. The components of this material include tetracalcium phosphate and dicalcium phosphate, which react in an aqueous environment to form hydroxyapatite, the mineral component of hard tissues. In contrast to calcium hydroxide, tetracalcium phosphate cement induced bridge formation with no superficial tissue necrosis and significant absence of pulp inflammation.¹⁴⁵

PULPOTOMY

The procedure has been described in detail in the section on apexogenesis/apexification.

PULPECTOMY

Rationale

Successful pulp therapy for primary teeth is one of the most valuable services a child patient can receive, since there is no better space maintainer than the retained primary tooth. The practitioner must be aware of the dangers of retaining untreated, carious primary molars. A carious molar left untreated merely invites chronic infection, which may at any time become an acute alveolar abscess. The possibility of hypoplasia or hypocalcification in the underlying teeth is also increased. Deflection of the eruption pathway is also possible. Orthodontic implications of premature loss of primary teeth are many.

Objectives

- Successful treatment of a cariously involved pulp.
- Maintaining the tooth in the oral cavity in a non pathogenic and healthy condition.
- Endodontically treated teeth should help in mastication and serve as natural space maintainers.
- Their retention helps in speech.
- Help in guidance to the developing dentition.

Anatomic Differences between Primary and Permanent Teeth

- Pulp chamber anatomy in primary teeth approximates the surface shape of the crown more closely than in permanent teeth.
- The pulps of primary teeth are proportionately larger and the pulp horns extend closer to the outer surfaces of the cusps than in permanent teeth.
- The dentin thickness is less than in permanent teeth.
- Increased numbers of accessory canals and foramina, as well as porosity of pulpal floors (Hibbard and Ireland, 1957).¹⁴⁶
- Roots are longer and more slender.
- Canals are more ribbon like with multiple pulp filaments within the more numerous accessory canals.
- Roots flare outwards to accommodate the succedaneous tooth bud.
- Roots tend to undergo physiologic root resorption as soon as root completion occurs, therefore, always in a state of flux.

Histologically

- Increased coronal cellularity and apical vascularity, therefore, increased healing capabilities.
- Fox and Heeley, 1980—No differences structurally between primary pulp tissue and young permanent pulp tissue with the exception of a cap like zone of reticular and collagenous fibres in the primary coronal pulp.¹⁴⁷

- Clinicians, however, have noted a difference in the pulp responses between the two.
- Primary teeth, generally, demonstrate an inflammatory response as opposed to the calcific scarring of permanent teeth.
- **Bernick**, 1959, found that in permanent teeth, pulp nerve fibres terminate among odontoblasts and even beyond the predentin. In primary teeth, they terminate in the odontoblastic layer.¹⁴⁸
- Also **Rapp et al**—Density of the innervation of primary teeth less than that of permanent teeth.¹⁴⁹
- Neural tissue is the first to degenerate when root resorption begins and the last to mature when the pulp develops.
- **McDonald**, 1956, reported that the localization of infection and inflammation is poorer in the primary pulp than that of permanent teeth.¹⁵⁰

Partial Pulpectomy

This procedure is called partial pulpectomy as complete negotiation of accessory canals is generally not achievable in primary teeth.

Indications of pulpectomy

- History of spontaneous pain at night.
- Intraoral swelling/sinus.
- History of extraoral swelling.
- Extensive bleeding from amputation site of radicular pulp tissue.
- Moderate mobility.
- Clinically evident carious exposure.
- Primary teeth with inflammation spreading beyond coronal pulp but no pathologic resorption of roots and alveolar bone.
- Primary teeth with necrotic pulps, minimum root resorption and minimum bony destruction in the bifurcation area.
- Pulpless primary teeth:
 - Without permanent successor
 - In hemophiliacs
 - Before eruption of 1st permanent molar
 - When speech, crowded arches or esthetics are a factor
 - Next to the line of a palatal cleft
 - Supporting orthodontic appliances
 - When arch length is deficient
 - When space maintainers or continued supervision is not feasible (handicapped/isolated children)

Radiographic indications (Fig. 2.44)

- Deep carious lesions extending upto the pulp confirmed by clinical evaluation
- Interradicular radiolucency evident on radiographs
- Pathologic root resorption not involving more than 1/3rd root
- Minimal destruction of bone support

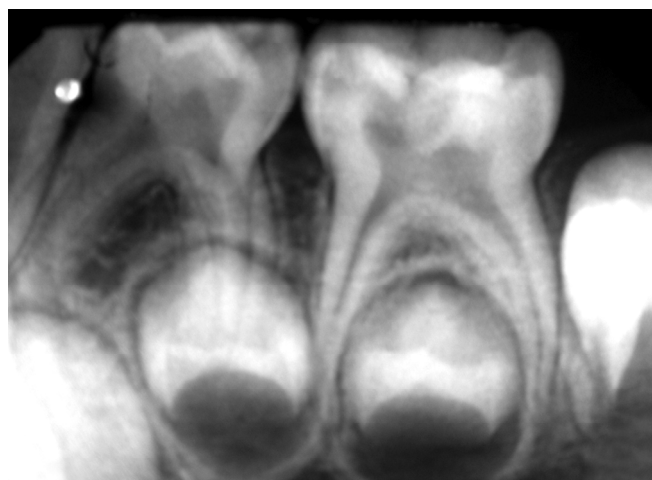


FIGURE 2.44: Preoperative radiograph of a deciduous mandibular second molar indicated for pulpectomy

Contraindications

- Teeth with non restorable crowns
- Periradicular involvement extending to the permanent tooth bud
- Pathologic resorption of >1/3rd root with a fistulous sinus tract
- Excessive internal resorption
- Extensive pulp floor opening into the bifurcation
- Primary teeth with underlying dentigerous or follicular cysts
- Young patients with systemic illness like congenital or rheumatic heart disease, hepatitis, leukemia, children on long term steroid therapy or immunocompromised.

Historical perspective

- **Sweet, 1930**—introduced the 4 to 5 step technique using formocresol for pulpless teeth with or without fistulae.¹⁵¹
- **Rabinowitz, 1953**—recommended 4 to 17 visits comprising 2 to 3 day application of formocresol in nonvital primary molars followed by precipitation of silver nitrate and a sealer of ZOE cement into the canals.¹⁵²
- **Gould, 1970**—worked upon primary molars in 3½ to 8½ year children. CMCP was placed in the pulp chamber for 5 minutes. ZOE was placed in the canals. 83% clinical and radiographic success was reported.¹⁵⁶
- **Hobson, 1970**—experimented with necrotic primary teeth whose canals were not debrided. Beechwood creosote was used for 2 weeks, then pulp chamber was filled with ZOE.¹⁵³
- **Vander Wall et al, 1972**—stated that formocresol is more effective than CMCP or Cresatin as a root canal medicament for inhibiting bacterial growth.¹⁶⁰
- **Lewis and Law, 1973**—practised conventional endodontics with sodium hypochlorite irrigation. Canals were medicated

for 3 to 7 days with eugenol, camphorated parachlorophenol or formocresol. During the second visit, canals were filled with ZOE or ZOE mixed with iodoform crystals.¹⁵⁴

- **Frigoletto, 1973**—stated that in asymptomatic necrotic primary teeth, canals should be debrided and irrigated with sodium hypochlorite. Canals were filled with root canal paste using a specially designed pressure syringe.¹⁵⁷
- **Starkey, 1980**—recommended a one appointment method for vital pulp—partial pulpectomy removing coronal aspect of the radicular pulp. He recommended a multiappointment method for necrotic pulps and periradicular involvement. Formocresol or CMCP was sealed with IRM for one week. Then canals are filled with ZOE.¹⁵⁸
- **Coll et al 1985**—reported an 80 to 86 percent success rate with the one sitting technique.¹⁵⁹
- **Barr et al 1986**—Observation period—40.2 months (approx. 3½ years)—85.5 percent success rate of primary molar pulpectomies. 88 percent show complete ZOE paste resorption. 25.8 percent reduction of preoperative radiolucencies.¹⁶¹
- **Flaitz et al 1989**—Observation period—37 months—68.5 percent successful pulpotomized anterior teeth and 84 percent successful pulpectomized anterior teeth.¹⁶²
- **Yacobi and Kenny, 1991**—Observation period—2 years—83 percent success rate for pulpectomized anterior teeth and 90 percent success rate for pulpectomized posterior teeth, probably due to more microleakage from composites in anterior teeth.¹⁶³
- **Judd and Kenny, 1991**—Recommended that H files (usually #20) be used for vital pulp extirpation and canals be filled with thin mix (toothpaste viscosity) of ZOE using a lentulospiral.¹⁵⁵

General Treatment Considerations

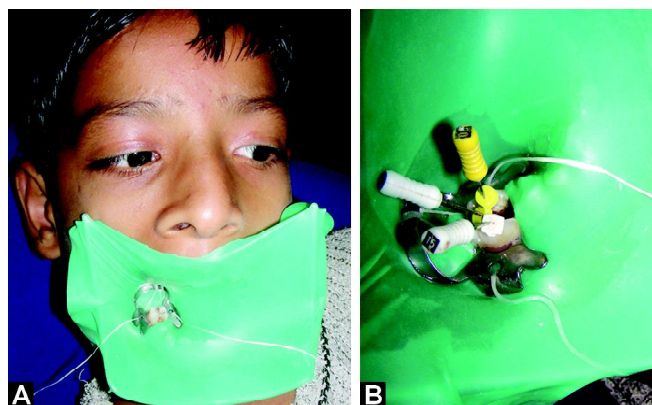
- Patient should be healthy and cooperative. In case of systemic disorders compromising a child's responses, the child's physician should be consulted.
- Informed consent should be obtained.

Dental Considerations

- Tooth must be restorable after root canal treatment.
- Chronologic and dental age must be evaluated to rule out teeth with imminent exfoliation.
- Psychological or cosmetic factors must be considered (may be more important to the parent).
- Number of teeth to be treated and strategic importance to the developing occlusion must be evaluated.
- Primary molar root anatomy, along with proximity of the underlying succedaneous tooth should be evaluated.

Procedure

- Adequate anesthesia is given.
- Rubber dam is applied.
- Dental caries removed completely.
- Enamel overhanging the coronal pulp removed for adequate access.
- Access cavity completed.
- Coronal pulp amputated upto the root canal orifice using a spoon excavator (e.g. API, Germany).
- Radicular pulp is removed with a fine barbed broach.
- H file or barbed broach for removal of pulp tissue remnants.
- Cleaning and shaping of canals preferably with K files as H files tend to fracture easily.
- Working length (Fig. 2.45)
 - (1 to 1.5 mm)—**Damle, 2006**¹⁶⁴
 - (2 to 3 mm)—**Dummett and Kopel**¹⁶⁵ short of the radiographic apex.
- Starting with a small sized file (#10), proceed in a sequential manner to a larger size (#35).
- Care should be taken that instruments do not extend periapically.
- Frequent irrigation is a must to allow debris to be flushed out.
- Irrigation with distilled water, saline, three percent hydrogen peroxide followed by 5.2 percent sodium hypochlorite.
- Canals dried using absorbent points.
- Canals filled with ZOE paste using incremental technique. Canals may be filled using a reamer and plugger
 - Absorbent points or a jiffy tube
 - A lentulospiral
 - Pressure syringes (Pulpdent Corporation, America). If pressure syringes are not available, a syringe with a tuberculin needle can be used.
- IOPA taken to evaluate the filling (Fig. 2.46).
- Restoration with miracle mix or amalgam followed by a stainless steel crown.



FIGURES 2.45A and B: Diagnostic instruments placed in the canals

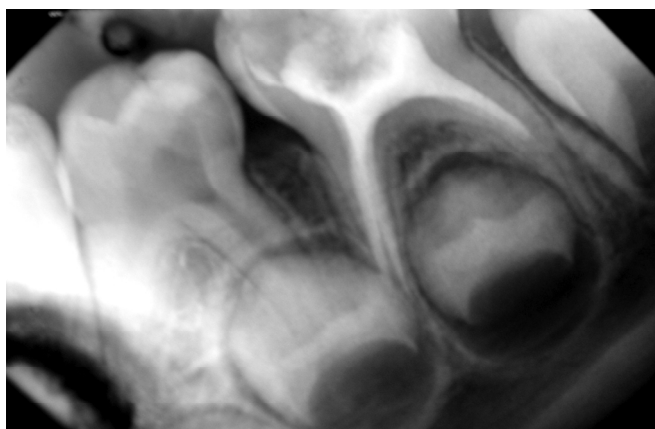


FIGURE 2.46: Canals obturated with zinc oxide eugenol

ROOT FILLING MATERIALS

Ideal Requirements

- Should resorb at a similar rate as the primary root.
- Should be harmless to the periapical tissues and to the permanent tooth germ and should resorb readily if pressed beyond the apex.
- Should have a stable disinfecting power.
- Should be inserted easily into the canal and be removed easily if necessary.
- Should adhere to the walls of the canal and should not shrink.
- Should not be soluble in water.
- Should not discolor the tooth.
- Should be radiopaque.

No material has been found till date which fulfills all of these criteria.

Commonly used materials are:

- Zinc oxide eugenol
- Iodoform paste
- Calcium hydroxide

Zinc Oxide Eugenol

Most commonly used filling material for primary teeth. Camp, 1984,¹⁶⁶ introduced endodontic pressure syringe to overcome the problem of underfilling, although, reports mention that as far back as 1961, Greenberg developed the pressure syringe for filling primary canals and this technique was described in detail by Spedding, 1977¹⁶⁷ and Krakow et al, 1981.¹⁶⁸

Underfilling is frequently clinically acceptable, as overfilling may cause a mild foreign body reaction.

Another disadvantage of ZOE is the difference between its rate of resorption and that of the tooth root.

Coll et al 1985, found that ZOE particle retention occurred in 8 of 17 patients followed till the time of premolar eruption.¹⁶⁹

Iodoform Paste

Commonly available:

Kri paste

Iodoform	80.8 percent
Camphor	4.86 percent
Parachlorophenol	2.025 percent
Menthol	1.215 percent

Maisto paste

Zinc oxide	14 gm
Iodoform	42 gm
Thymol	2 gm
Chlorophenol camphor	3 cc
Lanolin	0.5 gm

Barker and Lockett, 1971—identified the potential benefits of Kri paste, an iodoform compound.¹⁷⁰ Advantages are long lasting bactericidal properties, excellent resorbability and no undesirable effects on succedaneous teeth when used as a pulp canal medicament in abscessed primary teeth. It was noted that this paste would resorb within two weeks if found in the periradicular or furcation areas. An ingress of connective tissue was seen in the apical portions of the treated canals.

Since iodoform paste does not set into a hard mass, it can be removed if retreatment is required.

Holan and Fuks, 1993—clinically and radiographically compared Kri paste with ZOE after 48 months. 84 percent success with the Kri paste group v/s 65 percent success with the ZOE group was found.¹⁷¹

Garcia-Godoy, 1987—95.6 percent success clinically and radiographically with Kri paste during a 24 month period for 43 teeth.¹⁷²

Calcium Hydroxide

Several clinical and histopathologic investigations of calcium hydroxide and iodoform mixture have been published.

Vitapex (Neo Dental Chemical Products Co, Tokyo), **Endoflas** (Sanlon Laboratories, Columbia), **Metapex** are available.

Vitapex— Calcium hydroxide
Iodoform
Oily additives

It is harmless, and any overfilled material resorbs. It has been found to resorb at a slightly faster rate than the root. It has antiseptic properties, is radiopaque and can be easily removed in case of retreatment. It can be considered to be a nearly ideal primary tooth filling material. However, it is not generally recommended in vital pulp therapy in primary teeth.

Chawla et al 1998, have carried out a pilot study in the mandibular primary molars using calcium hydroxide paste as a root canal filling material and found it to be a success.¹⁷³

Tandon S et al observed almost a 100 percent clinical success in 10 endodontically treated primary molars which were filled with Vitapex (Calcium hydroxidised iodoform).¹⁷⁴

Gutta Percha

Since gutta percha is not a resorbable material, it is contraindicated in the primary teeth.

Recall

- Rate of success is generally high.
- Tooth should be periodically checked for normal resorption without interfering with the eruption of the permanent tooth.
- The primary tooth should remain asymptomatic, firm in the alveolus and free from pathosis. If evidence of pathosis is detected, extraction and conventional space maintenance are recommended.
- Occasionally, tooth may be overretained. Generally, large amount of ZOE in the pulp chamber may impair resorption. Management consists of simple removal of the crown and allowing the permanent tooth to erupt.

Criteria for Success

- Radiographically
 - No enlargement of periapical or furcation radiolucency
 - No pathologic resorption
 - Maintenance of normal PdL space and lamina dura
 - No damage to crypt of succedaneous tooth.
- Clinically
 - Patient asymptomatic
 - No extraoral/intraoral swelling/sinus (gumboil)
 - No pathologic mobility
 - No sensitivity on percussion/mastication.

APEXOGENESIS AND APEXIFICATION

Introduction

For many years, open apices, attributable to lack of maturation or resorption, have been treated inadequately by root canal fillings or by periapical surgery with a reverse amalgam filling. This situation is most frequently encountered in children and young adults. It is often best to treat immature teeth with a non-surgical approach because of the following reasons:

- In the surgical procedure, there is increased potential for interference with adjacent vital structures as this situation is most frequently encountered in children and young adults.

- Periapical surgery with beveling of the apex for adequate reverse amalgam placement further compromises an already increased crown-root ratio.
- Arens, 1977, has pointed out that the cementum of underdeveloped root tips is so weak and flimsy that it shatters like glass when it is contacted by a surgical bur.¹⁷⁴
- Psychological trauma of a surgical procedure.

APEXOGENESIS

Definitions

Weine, 1996—A pulpotomy procedure is indicated in the tooth with an open apex to allow completion of apical closure as long as the apical pulp remains vital. This is known as apexogenesis.¹⁷⁶

Walton and Torabinejad, 1989—Apexogenesis is defined as a treatment of vital pulp by pulp capping or pulpotomy in order to permit continued growth of root and continued closure of open apex.¹⁷⁷

Arens, 1977—Apexogenesis is defined as physiological root end development and formation.¹⁷⁵

Indications for Apexogenesis

- Reversible pulpitis from a deep carious lesion resulting in a mechanical exposure in a tooth with incompletely formed root apex.
- Irreversible pulpitis in a case of traumatic pulp exposure or a deep carious lesion involving the pulp of a young permanent tooth with an incompletely formed root but having a vital apical portion of the pulp.

Contraindications for Apexogenesis

- Tooth is sensitive to percussion or has a long history of pain indicates a long standing chronically inflamed pulp.
- Totally necrotic pulp or presence of sinus associated with the infected tooth.

Conventional Pulpotomy with Calcium Hydroxide

Technique

- The tooth is anesthetized and isolated with rubber dam.
- A conventional access is prepared with a high speed bur under aseptic conditions, using an air water coolant to minimize heat damage to the underlying pulp.
- Use of copious water spray and reduction of dentin in the floor of the access preparation to paper thinness before penetrating the pulp will minimize embedding of the dentinal debris in the remaining pulp tissues.
- After leaving paper thinness of the dentin, the roof of the pulp chamber is removed into its entirety with a sharp long

shank excavator in posterior teeth and a rotary instrument in anterior teeth.

- The cavity and the pulpal wound at its base are gently irrigated with sterile saline, sterile water or local anesthetic solution for 2 to 3 minutes until hemorrhage ceases. This will help prevent an extrapulpal blood clot forming over the wound surface as this has been shown to interfere with pulpal healing and detract from the prognosis.
- It may be necessary to saturate a cotton pellet with irrigant and apply to the surface with gentle pressure to control bleeding. Racemic epinephrine or any caustic chemical or medicament should not be used because the objective is to maintain the health of the remaining pulp.
- A suitable medicament or dressing (Calcium hydroxide) is placed on the remaining tissue in an attempt to promote healing and retention of this vital tissue. Calcium hydroxide hard setting pastes (commercially available as Life, Dycal, Pulpdent, etc.) are applied to the amputation site, if the amputation site is at the cervical line of the tooth. However, for deeper amputation, calcium hydroxide powder carried to the tooth in an amalgam carrier is the easiest method of application.
- A layer of intermediate restorative material (IRM) is placed over the calcium hydroxide.
- A permanent restoration is essential to the success of the apexogenesis procedure as temporary fillings invariably washout and leak over a period of time, resulting in bacterial contamination, often causing death of the pulp.
- A radiograph of the tooth is taken to serve as a basis for comparison with later films.

Recall procedure

- Includes the clinicoradiographic evaluation of the tooth.
- The total time taken for achievements of the goals of the apexogenesis pulpotomy ranges between 1 and 2 years, depending primarily upon the extent of tooth development at the time of pulpotomy procedure.
- The apexogenesis procedure differs from the apexification treatment in that the paste is not to be changed in the former whereas the paste may need to be changed numerous times in the latter.
- The patient should be recalled at a minimum of three month intervals after apexogenesis therapy in order to determine the vitality of the pulp and the extent of apical maturation.
- It is important to remember that the formation of the calcification is not always indicative of the success of the treatment and that, in some cases, apical maturation occurs in the absence of the calcific barrier. It is important not to allow the calcific barrier to enlarge in size and partially or totally obliterate the root canal, because it would then be difficult to gain access to the root canal and would impede endodontic treatment at a later date. An absence of

symptoms does not necessarily reflect the true state of the pulp. In instances of pulp capping and high (partial) pulpotomies, pulp testing may aid in determining the pulp's viability. Where a temporary crown has been placed, a small hole may be placed slightly incisally from the facial gingival margin to allow for pulp testing. However, in evaluating most pulpotomies, radiographic interpretation of pulpal and periapical pathosis or clinical symptoms of spontaneous pain, swelling, unusual discomfort from percussion and palpation and/or sinus tract formation are the major means of suggesting the status of the pulp. Caution should be observed in interpreting the normal radiographic radiolucency of the root sheath as periapical involvement. It has been suggested by Camp, that on numerous occasions, the electric pulp tester gave no response when testing uninvolved, incompletely developed permanent teeth.¹⁷⁸ Therefore, only a positive response is usually considered as valid.

Shallow/Partial Pulpotomy with Calcium Hydroxide

The shallow pulpotomy is the treatment of choice for impact trauma exposure on an anterior tooth. Cvek has reported that pulp capping and partial pulpotomy with calcium hydroxide on traumatically exposed pulps are successful 96 percent of the time.¹⁷⁹

The major advantages compared with total pulpotomy operation are:

- It conserves tooth structure
- It permits continued formation of dentin coronally
- It is simpler to perform

Technique

- The tooth is anesthetized and isolated with rubber dam.
- The exposed dentin is washed with a weak solution of sodium hypochlorite (or saline or anesthetic solution).
- The granulation tissue from the site of pulp exposure is removed.
- Gently and gradually, wipe away pulp tissue with a rotating, water-cooled round diamond bur in a high speed handpiece. Begin at the site of exposure and proceed to a depth of 2 mm but avoid the cervical level of pulp, if possible. The pulp in that area is important for dentin production, which will help strengthen the tooth and help prevent future cervical crown fracture.
- Gently wash the wound with saline and place a moist cotton pellet on the wound until bleeding stops.
- Dress the wound with a hard setting calcium hydroxide liner. Also cover the exposed dentin with the same liner.
- Place a thin mix of hard setting zinc phosphate cement over the liner.
- When the cement has set, the tooth can be restored with acid etched composite.

- Clinico-radiographic examination on recall should be followed diligently.

Prognosis: The prognosis of partial pulpotomy is uncertain because of the difficulty of diagnosing the state of the pulp and of maintaining the temporary restoration in some cases. However, partial pulpotomy gives better results than a direct pulp capping.

Formocresol Pulpotomy

Formalin containing compounds have been used in pulp therapy since the early days of the twentieth century. Formocresol was introduced in 1904 by Buckley, who contended that equal parts of formalin and tricresol would react chemically with the intermediate and end products of pulp inflammation to form a new, colorless and non-infective compound of harmless nature.¹⁸⁰ The formocresol pulpotomy technique used today is a modification of the original method reported by Sweet in 1930.¹⁸¹ This formula of Buckley consists of 35 percent tricresol, 19 percent formaldehyde, 15 percent water and glycerine.

Mechanism of action

- Formocresol is an efficient bactericide.
- It was also found to have the ability to prevent autolysis of tissue by the complex chemical binding of formaldehyde with protein which may be reversible.
- Massler and Mansukhani, 1959, conducted a detailed histologic investigation of the effect of formocresol on human pulps of primary and permanent teeth.¹⁸² Fixation of the tissue directly under medicament was apparent shortly after application (7 to 14 days). The pulps developed three distinctive zones:
 - A broad eosinophilic zone of fixation
 - A broad pale staining zone with poor cellular definition
 - A zone of inflammation diffusing apically into normal pulpal tissue.
- Formocresol pulpotomy was earlier regarded as non-vital or mummification method but subsequent clinical and histologic studies have raised a doubt about labeling the method as non-vital. Quiet a few investigators term the technique as vital (upto 5 min) or non-vital (3 days) according to the length of time of the application.
- The formocresol pulpotomy procedure has appeal because there is a lack of calcification of the remaining pulp tissue as is sometimes seen with calcium hydroxide pulpotomy.
- Hence, even though the calcium hydroxide pulpotomy has been recommended as the treatment of choice in the pulpally involved permanent tooth, evidence of continued apical development following formocresol pulpotomy procedures on young permanent teeth with incompletely developed apices has been reported.

Technique

- Anesthetize the tooth and isolate it using rubber dam (Fig. 2.47).
- Place a no. 330 bur in a high speed handpiece and gain occlusal access to the pulp. It is better to make too large an opening than one that is too small. Remove all overhanging enamel.
- Using a sterile no. 4 or no. 8 round bur (slow speed), remove all carious dentin, if possible, before exposing the pulp horns.
- With a slow or high speed bur connect the pulp horns and expose the pulp.
- Excise the pulp tissue to the orifices of the root canals.
- Use a large spoon excavator to remove any remaining pulpal tissue. Gently wash out the debris with a water syringe (Fig. 2.48).
- Evaluate the hemorrhage. A vital pulp with minimal chronic inflammation should achieve hemostasis in 3 to 5 min. If there is chronic hemorrhage, check for remaining pulpal tissue in the pulp chamber. If there is purulent exudate, fibrotic pulp or uncontrollable hemorrhage, consider alternative pulp procedures.
- Place a sterile cotton pellet moistened (not saturated) with 20 percent dilution formocresol on the exposed pulp stumps. Place a dry pellet over the first pellet to maximize contact with the pulpal tissue and leave for 2 min (Fig. 2.49).
- On removal, the pulp stump should appear blackish brown. If there is bleeding, check for residual pulpal tissue. Reapply formocresol for 2 min.
- Fill the chamber to about half its volume with the thick mixture of zinc oxide eugenol. Some clinicians advocate adding equal drops of formocresol to the eugenol, then mixing with zinc oxide powder.

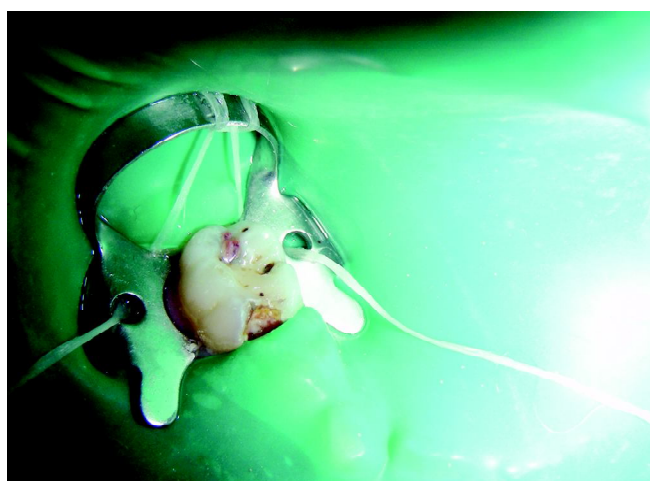


FIGURE 2.47: Preoperative view of a deciduous mandibular second molar indicated for pulpotomy

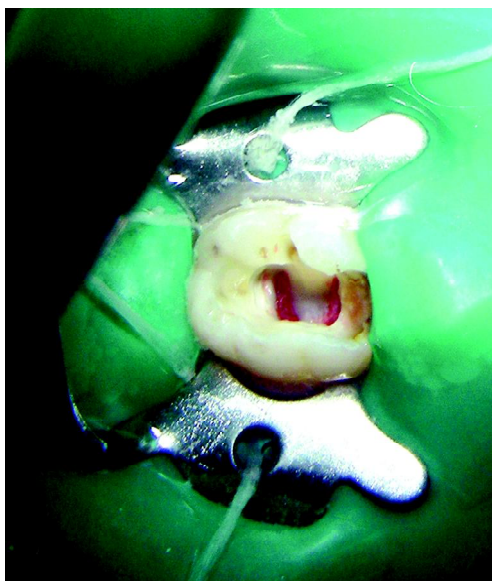


FIGURE 2.48: Bleeding points seen after removal of coronal pulp



FIGURE 2.49: Pulp stumps seen after application of formocresol

- A permanent restoration of amalgam or stainless steel crown is of choice (Fig. 2.50).

Other materials used for pulpotomy are cresatin, Ledermix, glutaraldehyde.

APEXIFICATION

Definitions

American Association of Endodontists, 1981—Apexification is a method of inducing apical closure by the formation of osteocementum or a similar hard tissue or the continued apical



FIGURE 2.50: Radiographic view of formocresol pulpotomy after placement of stainless steel crown

development of the roots of an incompletely formed tooth in which the pulp is no longer vital.

Nicholls, 1992—Apexification is a method of inducing apical closure through formation of mineralized tissue in the apical pulp region of a non-vital pulp with an incompletely formed apex.

Technique

First appointment

- In all patients in whom acute clinical symptoms are present, emergency endodontic procedures should be carried out before starting root induction. Once the patient is asymptomatic, the following treatment sequence can be used.
- Anesthetize the tooth and isolate using the rubber dam.
- Establish a conventional access.
- Debride the coronal two thirds of the canal with broaches and large Hedstrom files.
- Irrigate the canal thoroughly with an acceptable endodontic irrigant such as 2.5 percent sodium hypochlorite.
- Dry the canal that is approached with files, using large sterile absorbent points.
- Medicate the canal with camphorated monochlorophenol (CMCP).
- Temporarily seal the chamber with Cavit.

Second appointment

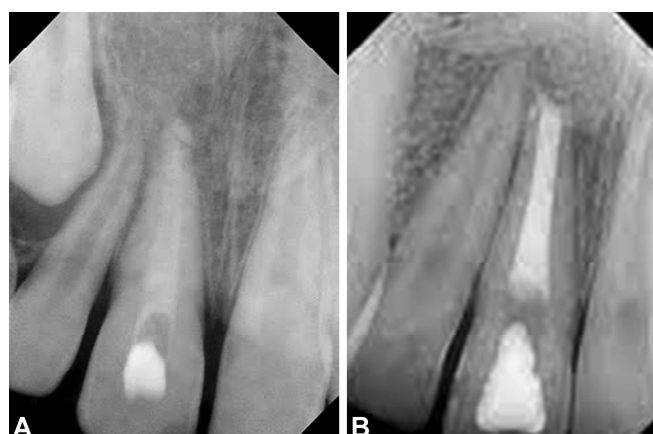
- Place a rubber dam and remove the temporary filling.
- Irrigate the canal thoroughly.
- Establish the working length. Since the canal walls in the apical region may be paper thin, there is probably some advantage to establishing the working length approximately 2 mm coronal to the most apical root edge. By working at

this slightly coronal level, there is less likelihood that the thin apical root structure will be torn by files. By restricting filing to within the root canal, there is also less likelihood that periapical tissue that may still have the potential to participate in further root development will be damaged; hence, additional root structure may form apical to the level to which one ultimately places calcium hydroxide.

- Instrument the canal; large sized (# 70 to #90) Hedstrom files) are recommended. Instrumentation in these instances should be thought of as planing of all walls of the canal without an attempt to increase the size of the canal.
- Dry the canal with coarse sterile paper points, held at the working length so that the point does not go beyond the canal.
- Medicate the canal with CMCP.
- The access cavity is then sealed with Cavit.

Third appointment

- Place the rubber dam and remove the Cavit and medicated pellet.
- Freshen the canal walls with the same size file used at the second appointment, and then thoroughly irrigate the canal again to remove debris.
- Dry the canal with absorbent points. Some bleeding may be encountered due to ingrowth of perapical inflammatory tissue. This may be controlled by irrigation and assuring that the paper points do not go beyond the working length. Slight bleeding that continues to dampen the apical canals should not, however, be of concern.
- Prepare the calcium hydroxide paste on a sterile glass slab, mixing USP calcium hydroxide powder with camphorated monochlorophenol. When mixed to proper consistency, the mass should have putty like thickness and should hold its shape when mounted on the slab. The paste can be carried into the canal with a sterile amalgam carrier. Alternatively, special syringes can be used to introduce the calcium paste into the canal.
- Begin moving the paste into the apical canal with the long plugger that can be introduced to within 2 to 3 mm of the working length without binding on any of the canal walls. Although material that is forced beyond the canal into periapical tissue will generally resorb, it is desirable to attempt to confine the calcium hydroxide paste to the root canal.
- Then, additional paste can be placed in the canal and the condensation procedure repeated. As the canal begins to fill it may be helpful to use a larger size plugger than the one you used for the initial condensation. Although pluggers work well, some operators prefer to tamp the paste in place with the butt ends of large sized paper points.
- A radiograph should be taken to assess the quality of the obturation. Although the calcium hydroxide paste does not



FIGURES 2.51A and B: Radiographic appearance of apexification after placement of calcium hydroxide in a maxillary central incisor and after obturation with gutta-percha

have the radiopacity of conventional root canal filling materials, you should begin to lose the clarity of the canal outline when the material has been properly condensed (Figs 2.51A and B).

- Excess paste should be removed from the chamber with a spoon excavator and a suitable intermediate restorative material should be placed in the access cavity.
- Another technique for the paste placement by Teplitsky, 1986, using the compactor, as originally used by McSpadden for canal filling has been described.¹⁸³

Refilling Procedure

- For a more predictable result, the calcium hydroxide would be changed routinely at the first 6-week observation visit.
- Holland et al, 1979, demonstrated better results with the change of paste. They speculated that the refilling process caused contact with a developed connective tissue rather than with the blood clot, whereas previous researchers demonstrated unsuccessful cases when a blood clot was present between the calcium hydroxide and vital pulp tissue.¹⁸⁴
- The paste is removed with an endodontic instrument approximately half the diameter of the canal with a reaming motion followed subsequently by copious irrigation with sterile water or saline.
- Often the incisal half of paste filling is dry but the apical half is wet (mushy).
- After drying the canal a new calcium hydroxide paste is vertically condensed exercising care to confine the paste to the canal system.

Recall

- Ultimately, a bridge of hard tissue in the apical 1 to 2 mm is desired in apexification therapy.

- As a general rule, the patient should be recalled 6 weeks following the second paste placement and approximately 2 to 3 months thereafter until a calcified deposition is complete.
- The total time of treatment averages 12 to 18 months but may vary from a few months to a couple of years, depending primarily on the status of the root closure at the time of initial treatment.
- If there appears to be a dilution of paste in the canal (e.g. it becomes more radiolucent) when checked on recall, the calcium hydroxide should be changed.
- At six months, the patient is recalled for radiographic examination again. One of the following five apical conditions will be found:
 - No radiographic change is apparent but if an instrument is inserted, a blockage at the apex will be encountered.
 - Radiographic evidence of a calcified material is seen at or near the apex. In some cases degree of calcification might be extremely extensive.
 - Apex closes without any change in the canal space.
 - Apex continues to develop with closure of the canal.
 - No radiographic evidence of change is seen and clinical symptoms and/or development of periapical lesion occur.
- Confirmation of a calcific deposit by light finger pressure with smaller files.
- Drying of the canal system with paper points eliciting no hemorrhage or tissue fluids.
- Obturation of the root canal system with gutta-percha can be accomplished successfully with either of the following techniques:
 - The Warm (Vertical) Gutta-percha technique (Schilder, 1983)—the large canal system and the blunderbuss apex in many of these teeth may indicate that the incremental warm gutta-percha technique is more desirable.¹⁸⁵
 - The Lateral Condensation technique—As many of these canals are irregular and larger than the largest size gutta-percha cone available (140), a customized gutta percha cone will need to be fabricated. Ingle, 1976, suggests rolling two or more gutta-percha cones together between a cool glass slab and one that is heated to create the desired size and shape of the master cone.¹⁸⁶
- Because the calcific deposit is of porous nature, extrusion of the root canal cement may be seen as a result of proper condensation pressure applied to the gutta-percha filling.
- However, the bridging will confine the gutta-percha to the root canal system.
- As with all endodontic fillings, the patient should be recalled at 6 and 12 month intervals for reevaluation.

Final filling of the root canal system

- Remove the calcium hydroxide paste and irrigate the canals.
- Instrumentations should extend only till the calcific barrier which may be 1 to 2 mm short of the initial treatment length because of the thickness of the barrier.
- Canal may be enlarged by two instrument sizes to remove calcium hydroxide remnants, critically judging this step with the relative thinness of dentinal walls of immature teeth.
- The final determination of readiness to obturate with gutta-percha is predicted on the following criteria:
 - Symptomless tooth with healing of any previous sinus tract or fistula.
 - Radiographic observation of osseous deposition in the periapical or lateral defect, if originally present. Often the calcific bridging does not occur until after the osteogenic healing which provides a matrix for hard tissue deposition.
 - Radiographic observation of hard tissue deposition at the apex, barium sulfate is often incorporated into this apical bridging, mimicking the paste filling.
 - Finding the calcium hydroxide paste to be dry when tested by probing with an endodontic instrument or explorer, suggesting that there is minimal fluid exchange between the root canal system and the periodontium.

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Pulp Pathologies in Children

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CHAPTER OVERVIEW

Introduction
Need to learn pulp pathology
Concept of pain
Neuroanatomy of pain
Behavior of dental pains
Causes of pulp pathology
Pulpal reaction to an insult
Reversible pulpitis
Hypersensitivity
Cracked tooth syndrome
Focal reversible pulpitis (Pulp hyperemia)

Acute pulpitis
Chronic pulpalgia (Subacute pulpitis)
Acute pulpitis with apical periodontitis
Nonpainful pulpitis
Pulpal granuloma
Chronic hyperplastic pulpitis
Irreversible pulpitis
Pulp degeneration
Pulp calcifications
Pulp necrosis

INTRODUCTION

The pulp has been described both as a highly resistant organ as well as an organ with little resistance or recuperating ability. The desirability of maintaining a vital pulp and protecting it from injury has been recognized by early practitioners. Dr. Grossman chronicled the historical events impacting on root canal therapy. He divided the 200 years between 1776 and 1976 into four 50-year periods.¹ During the first period, 1776 to 1826, he noted that treatment was crude - abscessed teeth were treated with leeches or toasted fig poultices and pulps were cauterized with red-hot wires. Nevertheless, it was during this same period that root canals were being filled from apex to crown with gold foil. The second half-century, 1826 to 1876, was marked by the founding of the first dental journal and the first dental school, the introduction of general anesthesia, rubber dam, gutta-percha, root canal points and the barbed broach, as well as three- and four-sided tapering broaches for cleaning and enlarging root canals, intracanal antiseptics, and oxyphosphate of zinc cement. At the same time, however, pulps were still being removed by driving wooden pegs into the canal, and crowns of the teeth were also being "snipped" off at the gingival level to cure toothache. Arsenicals were still being used

to devitalize pulps. The third half-century, 1876 to 1926, was highlighted by the discovery and development of the X-ray, the advent of local anesthetics, and the acceptance of antiseptics as a part of endodontic therapy. Beginning about 1912, dentistry in general and endodontics in particular were set back by the wide acceptance of the theory of focal infection. Wholesale extraction of both vital and pulpless teeth took place. The professions were not to recover their senses until well after World War II. The final 50-year period, 1926 to 1976, saw improvements in radiographs, anesthetics and procedures as well as the introduction of new methods and agents. Calcium hydroxide made its appearance, as did ethylenediaminetetraacetic acid (EDTA) for chelation. This period also witnessed the rise and decline of the silver root canal point. A more sensible attitude towards endodontic surgery developed.

During this period, the American Association of Endodontists (AAE) was formed, followed by the American Board of Endodontics. Continuing education in endodontics widely disseminated information, skills and techniques to an eager profession. The prevention of pulp disease began to play a more important role in dental practice. There was a decline

in dental caries, in part because of fluoridation. Research into the causes and biology of dental trauma led to improved awareness and treatment of dental injuries. Antibiotics greatly improved the profession's ability to control infection, while new anesthetics and injection techniques increased control over pain. The high-speed air rotor handpiece added to patient comfort and the speed and ease of operation, as did prepackaged sterilized supplies. The mandatory use of masks, gloves and better sterilizing methods rapidly emerged with the spread of Human immunodeficiency virus/Acquired immune deficiency syndrome (HIV/AIDS) and hepatitis. The widespread use of auxiliaries expanded dental services. All in all, the new millennium should prove exciting and profitable for the profession and patients alike.

NEED TO LEARN PULP PATHOLOGY

- To effectively treat endodontic infections, clinicians must recognize the cause and effect of microbial invasion of the dental pulp space and the surrounding periradicular tissues.
- Knowledge of the microorganisms associated with endodontic disease is necessary to develop a basic understanding of the disease process and a sound rationale for effective management of patients with endodontic infections.
- Proper diagnosis is the discipline that separates the really competent dentist from the merely mechanical; hence the extensive coverage of the subject.

CONCEPT OF PAIN

- Around 21.8 percent adults in US report with orofacial pain within a span of six months. In fact, it is the most common factor for seeking treatment.
- At the same time, fear remains the most common factor for avoiding treatment.
- It remains our duty as clinicians to diagnose the cause and source of orofacial pain, allay patient fears and render treatment suitable for the individual.

DEFINITIONS OF PAIN

- An unpleasant emotional and sensory experience associated with actual or potential tissue damage. Defines both physiologic and psychologic components.
- A more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings. It serves as a protective mechanism in so far as it induces the sufferer to remove or withdraw from the source.
- An unpleasant emotional experience usually initiated by a noxious stimulus and transmitted over a specialized neural network to the CNS where it is interpreted as such.

- Accurate knowledge of pain arising from dental or nondental sources is of utmost importance. Let us remember that there is no single cookbook therapy which is effective for pain; its management differs not only with the structural origin of pain but also with the psychological condition of the patient.
- Pain involves the following processes:²
 - Transduction
 - Transmission
 - Modulation and
 - Perception.

FUNCTIONAL NEUROANATOMY OF PAIN² (FIG. 3.1)

- The primary afferent neuron receives stimulus from the sensory receptor.
- This is carried to the CNS by way of the dorsal root to synapse in the dorsal horn of the spinal cord.
- Cell bodies of all the primary afferent neurons are located in the dorsal root ganglia.
- Second order neuron then carries it across to the anterolateral spinothalamic pathway.
- Between the first and second order neuron, multiple interneurons may be present.

THE FIRST ORDER NEURON

- Each receptor is attached to a first order neuron.
- **Clark et al 1935**, gave the relationship between diameter of nerve fibers and their conduction velocities.³
- Larger fibers conduct more rapidly than the smaller ones

Type A Nerve Fibers

- Alpha fibers
13–20 μm in diameter
70–120 m/s velocity

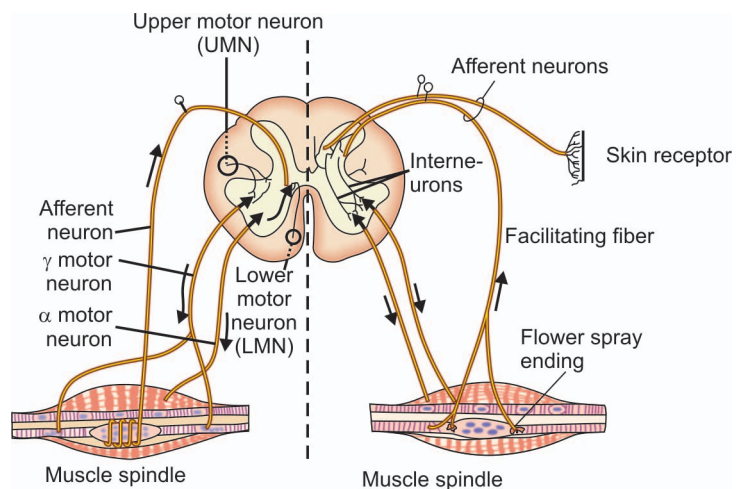


FIGURE 3.1: Functional neuroanatomy of pain

- Beta fibers
6–13 μm in diameter
40–70 m/s velocity
- Gamma fibers
3–8 μm in diameter
15–40 m/s velocity
- Delta fibers
1–5 μm in diameter
5–15 m/s velocity

Type C Nerve Fibers

- 0.5–1 μm in diameter
- 0.5–2 m/s velocity

Probable relationship between the fiber size and the type of impulse transmitted:

- A-alpha, A-beta, A-gamma carry impulses for tactile and proprioceptive responses.
- A-delta and C fibers conduct pain, but are not specific for it.

TYPES OF PAIN

- Pricking pain
- Burning pain
- A-delta fibers also conduct touch, warmth and cold
- C fibers also conduct itch, warmth and cold.

FIBERS DEMONSTRATE SPECIFICITY OF FUNCTION

- Fine peripheral nerve fibers can convey touch, pain, warmth and cold.
- Larger peripheral nerve fibers have specificity of function.

NOCICEPTIVE AFFERENT NEURONS

- Three classes:
 1. Mechano-thermal afferents—A-delta fibers—12–18 m/s. High degree of discriminative information. Peculiar to primates.
 2. Polymodal afferents—C fibers—0.5 m/s. Seen in all mammals.
 3. High threshold mechanoreceptive afferents—A-delta fibers. Present in all mammals. Can be sensitized by algogenic substances and responds to noxious heat.

MODULATION (FIGS 3.2 AND 3.3)

- The nociceptive specific second order neuron will cross the brain stem and ascend in the anterolateral tract on the opposite side.

- Impulses by A-delta fibers synapse in lamina I of the subnucleus caudalis.
- They then travel through the neospinothalamic tract to the thalamus.
- This results in *fast pain*.
- Impulses by C fibers synapse in Laminae II, III and V.
- They are carried through paleospinothalamic tract.
- They travel through interneurons into the reticular formation of the brain stem.
- From here, they travel to the thalamus.
- Impulse can be changed or modulated before it reaches the thalamus.
- This results in *slow pain*.
- Sharp pain—Easily localized, quick response.
- Slow pain—Suffering.
- C fibers contain substance P as the major neurotransmitter.
- Substance P persists at the synapse; hence progressive increase in intensity of slow chronic pain occurs.

PERCEPTION

- Determined by interaction of the cortex, thalamus, hypothalamus and limbic structures.
- Till now we have seen a mechanistic approach to pain.
- If treatment fails to alleviate pain, should the patient be considered neurotic? Such a situation probably indicates that researchers have still not completely unraveled the mystery of the human brain and its networking, nor that of pain perception.
- In perception occurs the addition of instincts, drives and emotions.
- This is influenced by past experiences and present environmental conditions.
- Hypothalamus prepares the body through responses of the ANS.

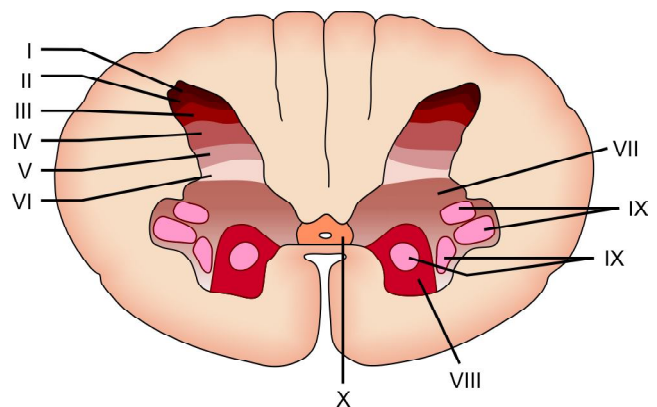
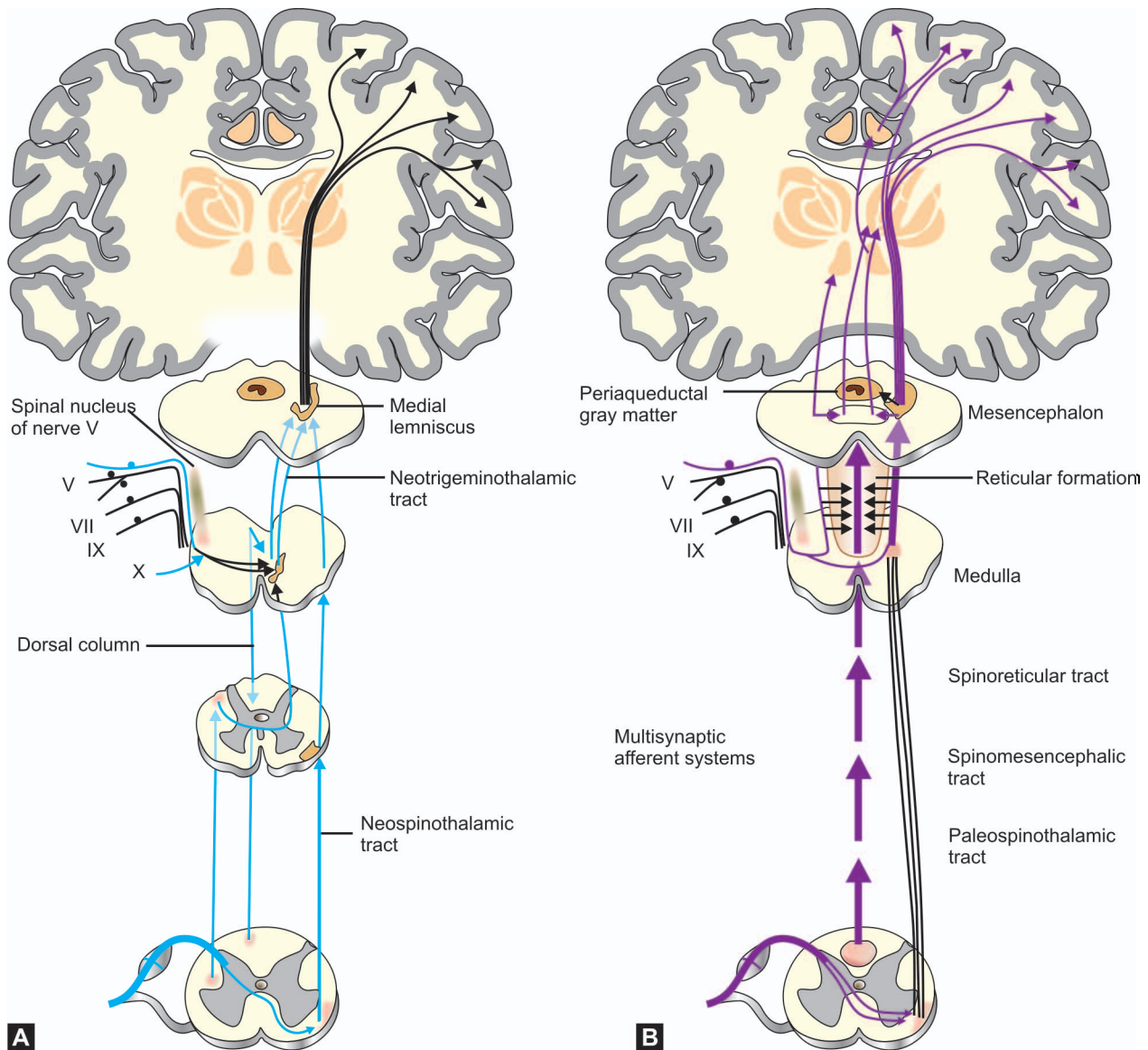


FIGURE 3.2: Cross section of the spinal cord showing various laminae



FIGURES 3.3A and B: Pain signals are transmitted to the brain by two main pathways. The lateral system (A) is made up of long thick fibers that transmit information about the onset of injury, and its precise location and intensity. They are designed to carry a rapid flow of pain signals to the thalamus to stimulate an immediate antinociceptive response. The medial system (B) is composed of phylogenetically older fibers that carry slower signals and probably transmit information related to the persistence of injury and level of response induced

- Hence, experience of pain is individual and personal,
- *Bio*—From somatic tissues (Figs 3.4 and 3.5).
- *Psychosocial*—interaction between thalamus, cortex and limbic structures (Figs 3.4 and 3.5).
- All neural function is based on neurotransmitter activity.
- There are two schools of thought here:
 1. Bio and psychological aspects are totally independent
 2. All activity has an organic neural basis.
- *Suffering* depends on an individual's psychology and may not be proportionally related to nociception or pain.
- *Pain behavior*, hence directly depends on the perception of pain and suffering of an individual.

SUBSTANCE P

- Polypeptide with 11 amino acids.
- Released at the central terminals of primary nociceptive neurons.
- Found at the distal terminals also.
- Excitatory neurotransmitter for nociceptive impulses.

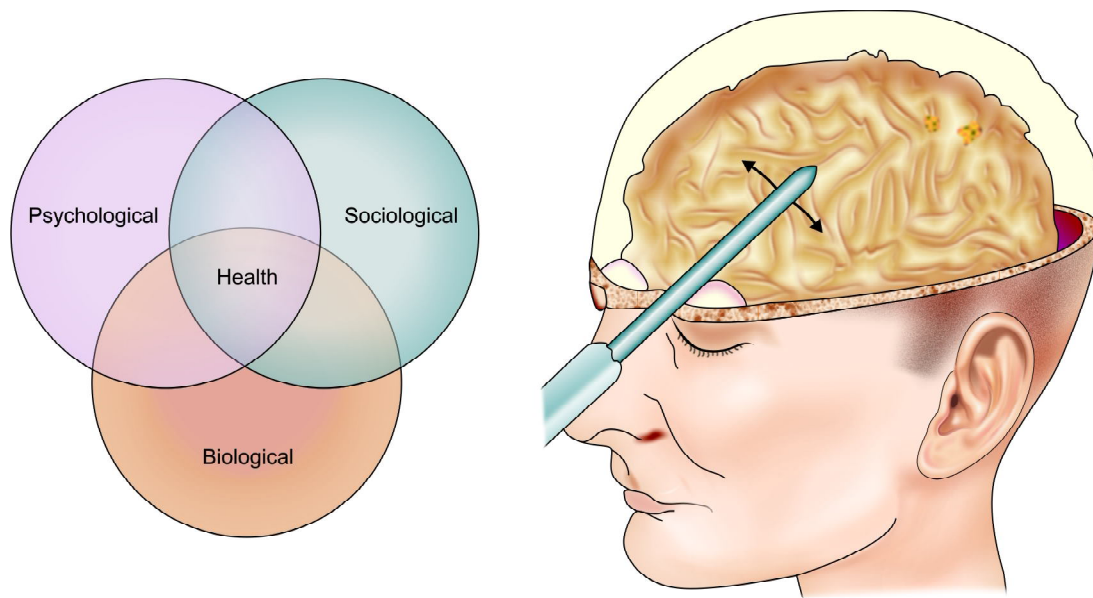


FIGURE 3.4: Biopsychosocial model of pain

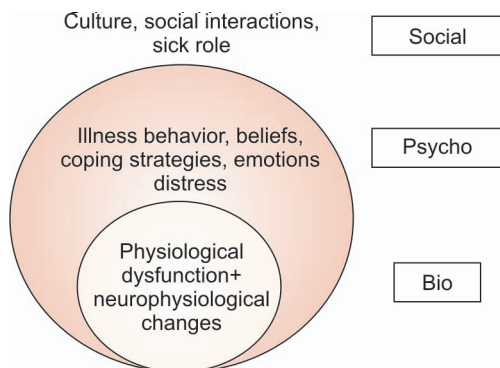


FIGURE 3.5: Diagrammatic representation of biopsychosocial model of pain

- Released from spinal cord cells by stimulation of A-delta and C fiber afferents.
- Excites neurons in the dorsal horn.
- Involved in neurogenic inflammatory phenomena.
- Content is highest in the most severely inflamed joints.

BEHAVIOR OF DENTAL PAIN

- The extreme variability of toothache affects the behaviour of dental pains.
- A good rule for any examiner is to consider all pains about the mouth and face to be of dental origin until proved otherwise.

PULPAL PAIN

- Visceral character
- Threshold type of pain
- Responds to impact, shock, thermal and chemical irritants, direct exploration
- Not to ordinary masticatory function
- Nonlocalizable by the subject.

CLASSIFICATION OF PULPAL PAIN

- Acute
- Chronic
- Recurrent
- Mixed with periodontal elements
- Nondental origin.

Acute Pulpal Pain

- Most typical of visceral pain
- Completely nonlocalizable
- Objective evidence required for diagnosis
- Protection is offered by tooth structure
- Only extreme surface irritation sensed as pain
- For example, split tooth results in acute pulpal pain.

Causes

- Threshold stimulation of the intact surface
- Cervical exposure due to gingival recession
- Splitting or fracture of the tooth

- Repeated thermal shocks transmitted by metallic fillings
- Thinning by erosion or abrasion
- Traumatic shock
- Dental caries.

Sequelae

- Inflammatory changes occur
- May be reversible or congestion



Pulpal necrosis



Gangrene

- Multirrooted teeth present a confusing symptom picture.
- Pain threshold is lowered by inflammation.
- Hypersensitivity also produces acute dental pain.
- Acute pulpal pain may range from occasional hypersensitivity to spontaneous violent throbbing toothache of intolerable intensity.
- It is increased by both heat and cold.

OR

Increased by heat, relieved by cold.

Recovery

- Pain ceases spontaneously.
- This could be due to transition from pulpal to periodontal involvement.
- If pulpal inflammation is due to infection, mixed pulpal and periodontal pains may occur due to development of an acute periodontal abscess.
- If pulpal inflammation is sterile, a painless periapical granuloma or radicular cyst may develop.

Chronic Pulpal Pain

- Inflammatory changes go into a chronic phase.
- There is neither resolution of the pulpal lesion nor necrosis.
- Chronic pulpitis may develop.
- Usually due to trauma to a young permanent tooth.
- Less responsive but positive to the pulp tester.
- Internal resorption may occur.
- Pain may be severe or mild.

Recurrent Pulpal Pain

- Recurrent pulpal pain rarely occurs.
- Inflammation usually follows either of two pathways: either it may resolve and pain may cease or it may change in nature leading to pulp necrosis, gangrene or periapical abscess.
- Examples are partially split tooth opened by some unusual occlusal stress.
- Recurrent hypersensitivity is a true example of recurrent pulpal pain.
- So called menstrual toothache and high altitude toothache.

Dental Pains of Periodontal Origin

- Deep somatic pain of the musculoskeletal type
- More localized in nature
- Responds in graduated increments
- Precise localization
- May be due to primary periodontal inflammatory condition
- May be due to dental therapy
- May spread from pulpal inflammation
- May extend from a nearby inflammatory condition.

Toothaches of Nondental Origin

- Dental pain is the most common orofacial pain. But heterotopic pains of variable etiology also do occur.
- Due to central sensitization or excitation of the second order neurons produced by a constant barrage of nociceptive input from deep structures.
- Local provocation, selective use of local anesthetic agents help in localization of pain.
- **Muscular toothache:** Usually pain from the muscles of mastication has a tendency to be referred to the teeth. Pain usually increases with mastication and appears as non-pulsatile, diffuse, dull and constant. Palpation of the muscle at specific trigger points may help in diagnosis of pain.
- **Neurovascular toothache:** Neurovascular toothache is usually brought on by stress. Most common type is migraine although tension type or cluster headache may be seen. Pain simulates pulpal pain with unilateral occurrence and periods of remission.
- **Cardiac toothache:** Cardiac pain is clinically characterized by heaviness, tightness or throbbing pain in the substernal region which commonly radiates to the left shoulder, arm, neck and mandible. It is the referred pain felt in the jaws with its origin in the cardiac region.
- **Neuropathic toothache:** Neuropathic pain is usually caused by abnormalities in the neural structures. It may occasionally be misdiagnosed as psychogenic pain as local factors cannot be visualized. Neuropathic pain may be seen as neuralgia, neuritis or neuropathy.
- **Sinus or nasal mucosal toothache:** Sinus or nasal mucosal toothache is usually expressed as pain in the maxillary and/or mandibular teeth. Signs and symptoms of sinusitis help in diagnosis along with aids like the paranasal sinus view, computed tomography imaging and nasal ultrasound.
- **Psychogenic toothache:** In psychogenic toothache no damage to any local tissue is evident. It is included in the category of mental disorders in which a patient may complain of a physical condition without the presence of any physical signs. All possible diagnoses must be ruled out before making the diagnosis of psychogenic toothache.

CLASSIFICATION OF PULPAL PATHOSES**LOYOLA UNIVERSITY**

1. Inflammatory changes
 - Hyperalgesia
 - Hypersensitive dentin
 - Hyperaemia
 - Acute pulpalgia (acute pulpitis)
 - Chronic pulpalgia (subacute pulpitis)
 - Chronic pulpitis
 - Chronic hyperplastic pulpitis
 - Pulp necrosis
2. Retrogressive (degenerative changes)
 - Atrophy
 - Dystrophic calcification

INGLE'S CLASSIFICATION

1. Inflammatory changes
 - Hyperreactive pulpalgia
 - Hypersensitivity
 - Hyperemia
 - Acute pulpalgia—incipient, moderate, advanced
 - Chronic pulpalgia
 - Hyperplastic pulpitis
 - Pulp necrosis
2. Retrogressive (degenerative changes)
 - Atrophic pulposis
 - Calcific pulposis

SELTZER AND BENDER'S CLASSIFICATION

1. Inflammatory changes
 - Intact pulp with scattered chronic inflammatory cells
 - Acute pulpitis
 - Chronic partial pulpitis with partial necrosis
 - Chronic partial pulpitis with partial liquefaction necrosis
 - Chronic partial pulpitis (hyperplastic form)
 - Pulp necrosis
2. Retrogressive (degenerative changes)
 - Atrophic pulp
 - Dystrophic mineralization

GROSSMAN'S CLASSIFICATION

1. Pulpitides
 - Reversible
 - Symptomatic
 - Asymptomatic
 - Irreversible
 - Acute
 - Abnormally responsive to cold

- Abnormally responsive to heat
 - Chronic
 - Asymptomatic with pulp exposure
 - Hyperplastic pulpitis
 - Internal resorption
2. Pulp degeneration
 - Calcific (Radiographic diagnosis)
 - Others (Histologic diagnosis)
 3. Necrosis.

CAUSES OF PULP PATHOLOGY⁴

1. Bacterial
 - A. Coronal ingress
 - Caries
 - Fracture
 - Complete
 - Incomplete (cracks, infraction)
 - Nonfracture trauma
 - Anomalous tract
 - Dens invaginatus (aka dens in dente)
 - Dens evaginatus
 - Radicular lingual groove (aka palatogingival groove)
 - B. Radicular ingress
 - Caries
 - Retrogenic infection
 - Periodontal pocket
 - Periodontal abscess
 - Hematogenic
2. Traumatic
 - A. Acute
 - Coronal fracture
 - Radicular fracture
 - Vascular stasis
 - Luxation
 - Avulsion
 - B. Chronic
 - Adolescent female bruxism
 - Traumatism
 - Attrition or abrasion
 - Erosion
3. Iatral
 - A. Cavity preparation
 - Heat of preparation
 - Depth of preparation
 - Dehydration
 - Pulp horn extensions
 - Pulp hemorrhage
 - Pulp exposure
 - Pin insertion
 - Impression taking

- B. Restoration
 - Insertion
 - Fracture
 - Complete
 - Incomplete
 - Force of cementing
 - Heat of polishing
- C. Intentional extirpation and root canal filling
- D. Orthodontic movement
- E. Periodontal curettage
- F. Electrosurgery
- G. Laser burn
- H. Periradicular curettage
- I. Rhinoplasty
- J. Osteotomy
- K. Intubation for general anesthesia
- 4. Chemical
 - A. Restorative materials
 - Cements
 - Plastics
 - Etching agents
 - Cavity liners
 - Dentin bonding agents
 - Tubule blockage agents
 - B. Disinfectants
 - Silver nitrate
 - Phenol
 - Sodium fluoride
 - C. Desiccants
 - Alcohol
 - Ether
 - Others
- 5. Idiopathic
 - A. Aging
 - B. Internal resorption
 - C. External resorption
 - D. Hereditary hypophosphatemia
 - E. Sickle cell anemia
 - F. Herpes zoster infection
 - G. Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS).

PULPAL REACTION TO AN INSULT

- Initial insult results in profound decrease in pulpal blood flow to the site of insult.
- Increase in flow of blood through arteriovenous anastomoses (AVA) occurs to reduce the amount of blood at the site of insult.
- Localized inflammatory lesions in the pulp occur (Fig. 3.6).
- Chemical mediators of inflammation are released in the vicinity.

- This results in vasodilatation due to increased vascular permeability.
- Decreased flow resistance occurs.
- Protein filtration occurs.
- Tissue becomes edematous.
- Venules are compressed.
- Blood flow becomes sluggish.
- Rheologic changes occur.
- Hypoxia prevails leading to impaired waste removal.
- **Van Hassel⁵** has explained the circumferential spread of inflammation.

COMPENSATORY MECHANISM

- AVA vessels open and shunt the blood.
- Increase in tissue pressure occurs.
- Macromolecules are pushed back into the bloodstream in a healthy region.
- Tissue pressure thus decreases back to the normal range.
- Restoration of normal blood flow occurs.

Response of the pulp to any insult depends on:

- Strength and duration of irritant
- Extent of pulp tissue affected
- Prior health status of the pulp.

CORONAL INGRESS OF BACTERIA

- Coronal caries is the most common means of ingress to the dental pulp.
- **Langeland, 1959**, noted pulp reactions in superficial fissure caries also.⁶
- **Brannstrom and Lind, 1965**, also noted pulp reaction in initial enamel caries with no evidence of radiographic penetration.⁷
- Only 60 percent caries is actually detected by radiographs, due to a variety of factors: either inherent limitations in the technique or operator related deficiencies.

Contradiction

- **Reeves and Stanley, 1966**, stated that little inflammation was observed with bacteria within 1.1 mm of pulp.⁸
- Inflammation increases when lesion reaches within 0.5 mm of the pulp.
- Generalized systemic bacteremia or anachoresis may occur with diffusion of the bacteria into the blood stream.

Permeability

- Dentin acts as a barrier but is permeable
- Most permeable—Dead tract dentin (Figs 3.7 and 3.8)
- Next—Primary dentin
- Less permeable—Irritation dentin.

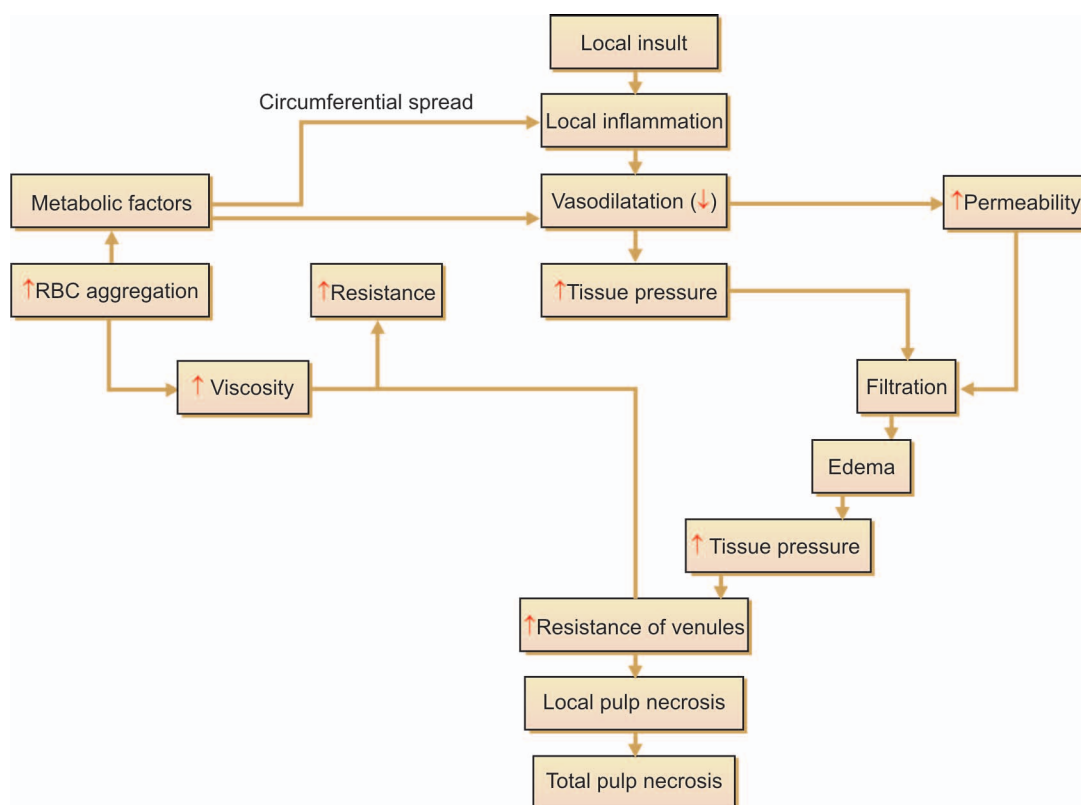


FIGURE 3.6: Circumferential spread of inflammation

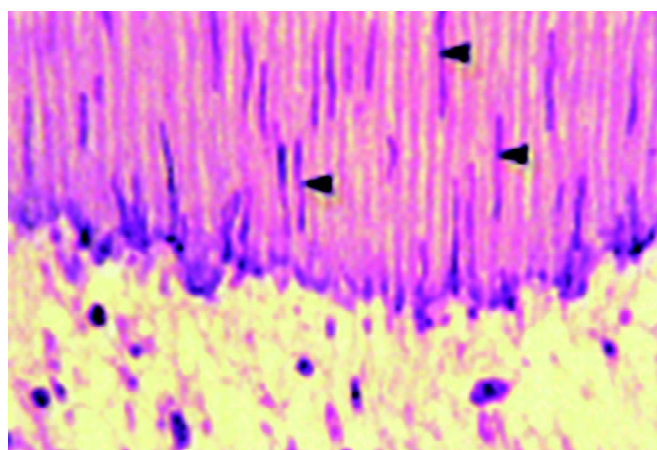


FIGURE 3.7: Bacteria penetrating through dentinal tubules

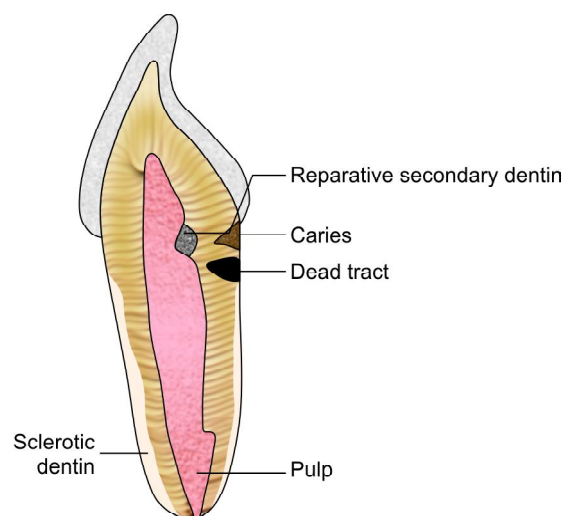


FIGURE 3.8: Dentin permeability after formation of dead tracts, sclerotic dentin, reparative dentin

Pulpal diffusion of microbial products depends on:

- Thickness of remaining dentin
- Surface area of exposed, permeable dentin
- Presence of a smear layer
- Potency of the microbial products
- Rate of pulpal blood flow.

PHYSICAL AGENTS AFFECTING THE PULP

- **Stanley, 1959**, stated that speeds of 50,000 rpm and greater are acceptable.
- 3000 to 30,000 rpm are most harmful to the pulp.⁹
- Effects of pulpal irritation are reduced by the production of irritational dentin.
- A remaining dentin thickness (RDT) of 2 mm is most suitable.
- **20 fold increase** in dentin permeability from RDT–3 mm to RDT–0.5 mm.
- Shortly after cutting there is an appreciable decrease in dentin permeability.
- **Kim, 1985**, stated that periodontal ligament injection should not be administered for anesthesia for restorative procedures in vital teeth as it alters the blood flow to the pulp and hampers the compensatory mechanism of the pulp.¹⁰

Thermal agents causing an insult to the pulp:

- Friction from cutting tools
 - Degree of frictional heat depends on:
 - i. Size and type of cutting tool
 - ii. Speed of rotation
 - iii. Cavity depth
 - iv. Effectiveness of coolant
- Metal fillings without proper insulation
- Heat during setting of cement
- During polishing of a restoration.

CHEMICAL AGENTS INSULTING THE PULP

- Disinfecting chemical applied to exposed dentin causes severe damage when RDT = 0.6 mm. Hydrogen peroxide may cause emboli and even arrest pulpal circulation, and hence is not currently recommended for disinfecting a prepared cavity.
- Dentin-conditioning and bonding agents
- Etchants
- Acid-liquid components of cements
 - GIC luting cement has a longer period of acidity than zinc phosphate or polycarboxylate but is more biocompatible to the pulp due to the larger size of polyacrylic molecules.
- Acrylic monomer
- Eugenol diffusion into the tubules may be beneficial or irritating.

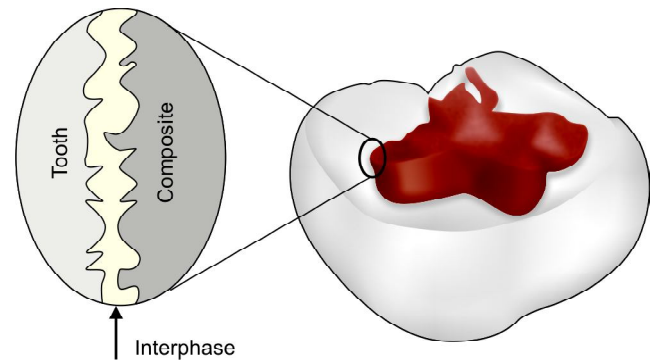


FIGURE 3.9: Diagrammatic representation of the interface between restoration and tooth

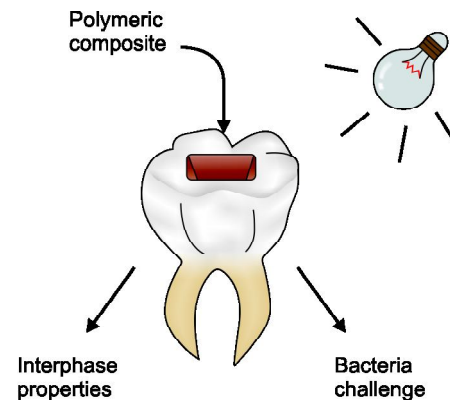


FIGURE 3.10: Factors affecting pulp reaction to a restoration

PULPAL REACTION TO RESTORATION (FIGS 3.9 AND 3.10)

- Chemical effects due to acidity of the restorative material.
- Microleakage through miniscule gaps in the restoration in which bacteria grow.
- Full crown restorations also exhibit some amount of leakage.
- Silicate > composite > amalgam > zinc oxide eugenol in terms of irritation to the pulpal tissue.
- ZOE most effective sealing agent against bacterial leakage.
- Factors affecting pulpal reaction to restoration:
 - Law of diffusion as applied to the dentin affects the reaction of the pulp to a restorative material.
 - Microleakage with a restoration.
 - Contraction gap of the restoration.
 - Tab on age of restoration.

Brannstrom, 1984, gave the following recommendations:¹¹

- Smear layer formed on dentinal cutting fosters bacteria, hence antibacterial detergent should be used to remove superficial smear layer.

- Residual smear plugs to be retained resulting in reduced permeability.
- Hydrophilic liner under restoration to be placed to counteract contraction gap.

REVERSIBLE PULPITIS

DEFINITION

Mild to moderate inflammatory condition of the pulp caused by noxious stimuli in which the pulp is capable of returning to an uninfamed state following removal of stimuli.

ETIOLOGY

Any noxious stimulus caused by trauma, disturbed occlusal relationship, thermal shock, etc.

PATHOGENESIS

- Acute inflammatory reactions are limited to the odontoblastic and sub-odontoblastic regions adjacent to the dentinal tubules involved.
- The odontoblastic nuclei may be displaced into the tubules due to increased local tissue pressure.
- The pulp tissue after repair is less vascular, less cellular and more fibrous than before, hence less able to withstand a subsequent insult.

CLINICAL FEATURES

- Sharp pain lasting for a moment.
- More often by cold food and beverages and cold air.
- Pain is not spontaneous in nature.
- Stops as soon as the cause is removed.
- Tooth responds to electric pulp testing at a lower current.

HISTOPATHOLOGIC FEATURES

- Ranges from hyperemia to mild to moderate inflammatory changes in the area of the involved dentinal tubules.
- Reparative dentin, disruption of the odontoblastic layer, dilated blood vessels, extravasation of fluids, immunological response may be seen.
- Chronic inflammatory cells with a few acute inflammatory cells are seen.

Management

1. Removal of noxious stimulus.
2. In case of caries, restoration of the tooth with an appropriate restorative material is indicated.

HYPERSENSITIVITY

DEFINITION

- Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentin in response to stimuli, typically thermal, evaporative, tactile, osmotic or chemical and which cannot be ascribed to any other dental defect or pathology.
- **Graf and Galasse, 1977**, reported that hypersensitivity affects 1 of 7 adult dental patients.¹²

ETIOPATHOGENESIS

- It is caused due to exposed dentinal tubules, leading to activation of A—delta fibers.
- The hydrodynamic theory is an excellent attempt at explaining the pathogenesis of hypersensitivity. This theory states that sensitivity is proportional to the hydraulic conductance of dentin.
 - *Hydrodynamic theory*: The dentinal tubules contain fluid called dental lymph. Fluid movement in the dentinal tubules stimulates the pain mechanism by mechanical disturbance of the nerve closely associated with the odontoblastic process. When dentin is exposed for the very first time, very small blebs of fluid are visible on the pulpal wall of the cavity or the wall of freshly cut dentin which is nearest to the pulp. If the cavity is dried using an air spray, more fluid is lost resulting in more fluid movement leading to more pain. Due to profuse branching of tubules at the dentino-enamel junction, the sensitivity is more. This is the most accepted theory of pain transmission through dentin.
- **Pashley, 1986**, stated that the most important variable is the condition of tubule aperture.¹³
- Intradental nerves may be affected with excess Na or K around the nerve terminal.
- This results in sensitivity to cold, air and heat presenting as pulpal pain.
- Inflammation of pulp occurs with excitation of C fibers leading to a release of CGRP (calcitonin gene related peptide) and substance P.
- Increase in blood flow and capillary permeability occurs.
- Low compliance results in an increase in tissue pressure.
- Due to this, mild changes in pressure will excite the intradental nerves resulting in a lowered threshold.
- In fact, **Trowbridge, 1985**, stated that hypersensitivity is the equivalent of sunburned skin.¹⁴

- Dentin sensitivity rather than hypersensitivity would be a more appropriate term, although both terms could be suitable.

Management

Certain chemical and physical agents have been used in the management of dentinal hypersensitivity.

- **Chemical agents**
 - Corticosteroids
 - Silver nitrate
 - Strontium chloride
 - Formaldehyde
 - Calcium hydroxide
 - Potassium nitrate
 - Fluorides
 - Sodium citrate
 - Iontophoresis with 2 percent sodium fluoride
 - Potassium oxalate.
- **Physical agents**
 - Composites
 - Resins
 - Varnishes
 - Sealants
 - Soft tissue grafts
 - Glass-ionomer cements
 - Lasers.

CRACKED TOOTH SYNDROME

- Why is it justified to call cracked tooth condition as a syndrome?
- Syndrome can be understood as *syn* means together and *dromos* means running along. Put together, it means an appearance of two or more features. Cracked tooth syndrome shows the following features:
 - Sharp, momentary pain on release of pressure.
 - Patient complains of pain ranging from mild to excruciating, at the initiation or release of biting pressure.
 - Crack in the tooth may involve enamel and dentin or may even involve pulp.
 - Pain mostly due to fluid movement in dentinal tubules causing stimulation of sub-odontoblastic nerve fibers.
- Crack can be visualized by using a dye or by trans-illuminating the tooth with fiber-optic light or by selective biting pressure on cotton roll or small wooden stick or rubber.

Management

1. Splinting of the offending cusp with cusp protecting restoration.
2. Removing the split cusp and restoring the tooth.

FOCAL REVERSIBLE PULPITIS / PULP HYPEREMIA

- Excessive accumulation of blood within the pulp tissue leading to vascular congestion.
- Capillary bed engorgement with a predisposition to edema due to prolonged vasodilatation.

PATHOPHYSIOLOGY (FIG. 3.11)

- Dentin is the permeable intermediary between the pulp and the enamel and cementum.
- Due to the bidirectional patency of the tubules, permeability is a major factor in the etiology of hyperaemia.
- Increase in the number of open dentinal tubules increases the dentin permeability.
- Permeability $\propto r^4$, where r = radius of a dentinal tubule.
- Permeability $1/\alpha$ length of the dentinal tubule.
- Pulpal disease state

$$= \frac{\text{Number of organisms} \times \text{Virulence}}{\text{Tissue resistance}}$$

- **Sarnat and Massler, 1965**, stated that caries may be active or arrested. Arrested caries usually has a sclerotic zone in dentin. Hence shows a less incidence of pulp hyperemia.¹⁵
- Pulp hyperemia is a potentially reversible response.

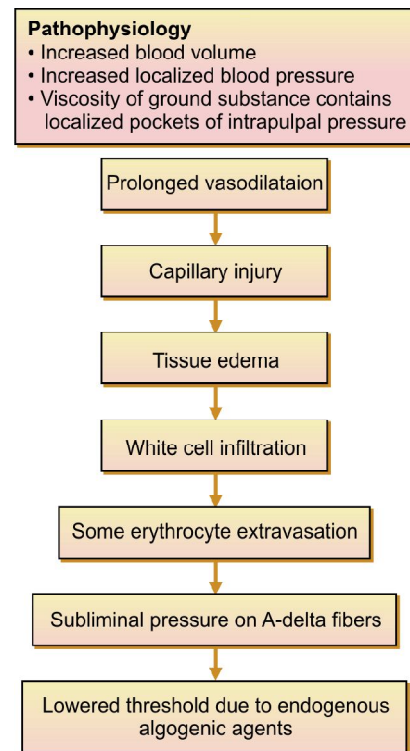


FIGURE 3.11: Pathophysiology of pulp hyperemia

CLINICAL FEATURES (SIMILAR TO REVERSIBLE PULPITIS)

- Sensitive to thermal changes, mainly cold.
- Pain disappears on removal of cold stimulus.
- Tooth responds to electric pulp testing at a lower current.
- Tooth usually shows a deep carious lesion or a large metallic restoration or a restoration with defective margins.

HISTOPATHOLOGIC FEATURES

- Acute extravasation of RBCs and some diapedesis of WBCs.
- Slowing of blood flow and hemoconcentration may result in thrombosis.
- Engorged pulpal vessels (Fig. 3.12).
- Cell free zone obscured by inflammatory cells.
- Small hemorrhages present in the pulp.
- Dentinoblastic layer partially disrupted.
- If prolonged insult, predentin is decreased in width.

Management

Removal of pulp irritants before the pulp is severely damaged.

ACUTE PULPITIS

Extensive inflammation of the pulp, it is a frequent sequel of focal reversible pulpitis.

ETIOLOGY

- Usually occurs in a tooth with a large carious lesion or a defective restoration or secondary caries.

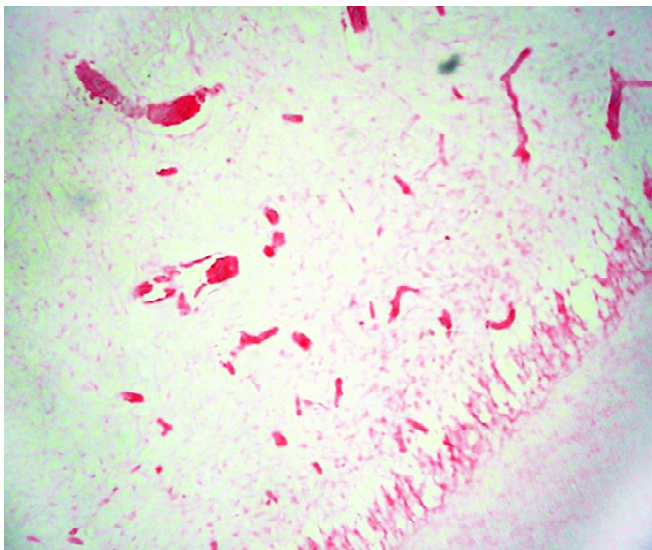


FIGURE 3.12: Pulp hyperemia showing engorged blood vessels

- Pulp exposure caused by a faulty cavity preparation.
- Trauma to tooth or cracked tooth syndrome.
- Also may be due to acute exacerbation of chronic inflammatory process.

CLINICAL FEATURES

- Severe pain due to thermal changes.
- Pain does not subside on removal of the stimulus.
- Severity of pain increases with time, may be described as lancinating.
- Intensity of pain increases on lying down.
- Application of heat may cause acute exacerbation of pain.
- Tooth reacts to the electronic pulp tester at a lower level of current.
- Pain present due to lack of escape of the inflammatory exudate and increase in intrapulpal pressure.
- Patient extremely uncomfortable and mildly ill.
- Pain from a vital pulp without tenderness to percussion.

HISTOPATHOLOGIC FEATURES

- Pulp may show chronic nature.
- Pulp could be in a serous stage, suppurative stage or a combination.
- Exudation closest to the point of irritation results in the acute symptoms.
- Vasodilatation, fluid exudation and leukocyte infiltration.
- Inflammation confined to coronal pulp.
- Localized destruction of pulp tissue and formation of pulp abscess.
- Pulp abscess seen as a small void surrounded by a dense band of leukocytic infiltration.
- Odontoblasts near the abscess undergo degeneration.

Management

1. Depending on whether the pathologic process is reversible or irreversible, treatment is palliative or invasive.
2. Treatment required is judged by knowledge of inflammatory spread in pulp and its non-compliant nature; this may include a vital or nonvital pulpotomy or a pulpectomy.

CHRONIC PULPALGIA (SUBACUTE PULPITIS)

CLINICAL FEATURES

- Intermittent episodes of mild to moderate pain by transient pressures from the exudative zone.
- Sometimes described as a smouldering inflammatory response.
- Word "grumble" used when describing discomfort from chronic pulpalgia.

- Throbbing pain due to pulsations.
- Only peaks of pulses reach suprathreshold levels.
- Later spontaneous, constant pain.
- If trigger is present, pain continues on removal of the irritant.

HISTOPATHOLOGIC FEATURES

- Prolonged dilation and engorgement—hyperemia.
- Increased vascular permeability.
- Fluid exudation.
- Increased protein content in tissue spaces.
- Leukocyte infiltration.
- Localized abscess formation.
- Injured and dead cells and products of proteolysis act as secondary irritants of the pulp.
- Phagocytosis and autolysis occurs.
- Suppurative core is formed.
- By this stage partial necrosis occurs.

Management

1. Depending on whether the pathologic process is reversible or irreversible, treatment is palliative or invasive.
2. In initial conditions, removal of the causative factor may result in resolution of the pain.
3. In later stages, pulp therapy may be required.

ACUTE PULPITIS WITH APICAL PERIODONTITIS

CLINICAL FEATURES

- Tooth tender to percussion.
- Heat causes intense pain.
- Cold relieves the pain.
- May be sensitive to both heat and cold.
- Inflammatory response extends to the periapex.
- Both pain and pressure receptors respond with pain.
- Periapex may be normal; frequently, widening of PDL space seen.

Management

Complete pulpectomy required or pulp near the apex must be removed to relieve pain.

NONPAINFUL PULPITIS

In nonpainful pulpitis, proliferative/chronic forces are hyperactive. There is decreased exudative inflammatory activity, hence decrease in intrapulpal pressure.

The exudative products:

- Are absorbed into circulation.
- Spread/point into adjacent connective tissue.
- Drain into the carious lesion.
- A combination of the above.

CLINICAL FEATURES

- Pain is not a prominent feature, but if present, is dull aching in nature, more often intermittent than continuous.
- Response to electric pulp vitality tester is reduced.
- Pulp tissue may be exposed.

HISTOPATHOLOGIC FEATURES

- Sclerotic and irritation dentin produced.
- Slow moving caries starts destroying the dentinal barrier.
- Pulp finally exposed.
- Similar process of inflammation.
- Zones of necrosis/infection, contamination, irritation/proliferation are seen (Fig. 3.13).
- Healing response shows formation of repair tissue.

Management

Pulpectomy or root canal treatment followed by crown restoration.

PULPAL GRANULOMA

- Granulomatous tissue formed, not just granulation tissue.
- **Kronfeld's** mountain pass concept, 1939—mainly for periapical granuloma.¹⁷ Kronfeld has explained that a granuloma does not favour the growth of bacteria. He compared the bacteria in the root canal with an army entrenched behind 'high and inaccessible mountains', the foramina serving as mountain passes. The exudative and

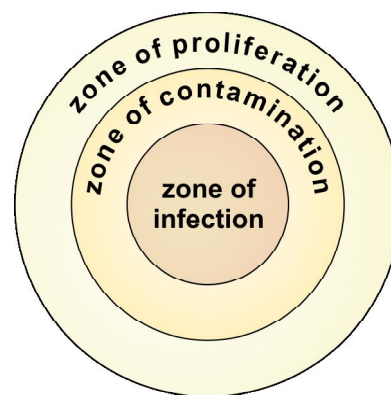


FIGURE 3.13: Zones of inflammation in the pulp described by Fish¹⁶

granulomatous tissue of the granuloma represents a mobilized army defending the plains (periapex) from the invaders (bacteria). When a few invaders enter the plain through the mountain pass, they are destroyed by the defenders (leucocytes). A mass attack of invaders results in a major battle analogous to acute inflammation. Only complete elimination of the invaders from their mountainous entrenchment will eliminate the need for a defence force in the 'plains'. Once this is accomplished, the defending army of leucocytes withdraws, the local destruction created by the battle is repaired, and the environment returns to its normal pattern.

CHRONIC HYPERPLASTIC PULPITIS

- Also called as “pulp polyp” or “pulpitis aperta”.
- Productive pulpal inflammation due to an extensive carious exposure of young pulp.
- Characterized by the development of granulation tissue, covered at times by epithelium and resulting from long standing low grade infection.

ETIOLOGY

- Slow progressive carious exposure of pulp.
- A large open cavity, young resistant pulp and chronic low grade stimulus is necessary.
- Mechanical irritation from chewing and bacterial infection also provides stimuli.

CLINICAL FEATURES

- Most commonly involved are deciduous molars and first permanent molars as they have an excellent blood supply because of large root opening, coupled with high tissue resistance and reactivity in young persons.
- Seen in children and young adults.
- Appears as a red fleshy pulpal mass filling the pulp chamber or cavity or extending beyond the confines of tooth (Figs 3.14 and 3.15).
- Relatively nonpainful to touch.
- May cause discomfort during mastication.
- Bleeds easily due to rich network of blood vessels.

HISTOPATHOLOGIC FEATURES

- Surface covered by stratified squamous epithelium.
- Epithelium derived from
 - Gingiva
 - Freshly desquamated epithelial cells of oral mucosa or tongue.
- Granulation tissue projects from the pulp into carious lesion.
- Granulation tissue is vascular containing collagen fibers, blood vessels, inflammatory cell infiltrate chiefly consisting of neutrophils, plasma cells and lymphocytes (Fig. 3.16).



FIGURE 3.14: Deciduous mandibular right second molar showing a pulp polyp



FIGURE 3.15: Specimen of a deciduous mandibular molar with a pulp polyp

- Due to absence of nerve endings, pain occurs only on pressure from mastication.

Management

Depending on the progress of the pathologic process, extirpation of pulp or extraction of the tooth may be required.

IRREVERSIBLE PULPITIS

Persistent inflammatory condition of the pulp, which may be symptomatic or asymptomatic and is caused by noxious stimuli.

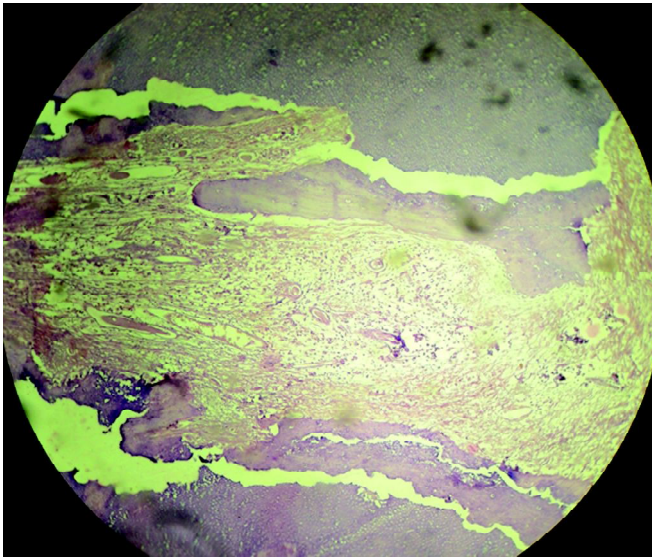


FIGURE 3.16: Carious dentin on the edges of soft tissue growth projecting from the carious lesion, the pulp chamber being highly vascular and has abundant chronic inflammatory cell infiltrate

ETIOLOGY

- Bacterial involvement of pulp through caries.
- Chemical, thermal or mechanical injury may also be the cause.

CLINICAL FEATURES

- Pain may be caused by sudden temperature changes like cold, sweet and acid foodstuffs.
- Pain continues after removal of cause.
- Pain is sharp, piercing or shooting. Pain may be intermittent or continuous.
- Change of position or posture exacerbates the pain due to change in intrapulpal pressure. Patient may stay awake at night due to pain brought about by change in posture.
- Pain may radiate to sinuses in case of upper teeth involvement or to the angle of mandible if lower teeth are involved.
- In later stages, pain is more severe and generally gnawing or throbbing.
- Pain increased by heat and relieved by cold.

HISTOPATHOLOGIC FEATURES

- Chronic inflammatory response may be seen in pulpal tissue.
- Postcapillary venules get engorged, necrosis of pulp.
- Necrotic areas attract polymorphonuclear leukocytes.
- Necrotic debris, dead cells form pus.
- Various areas of microabscesses are formed lined by fibrous wall.

Management

Complete removal of pulp and placement of intracanal medicaments like cresatin, eugenol or formocresol.

PULP DEGENERATION

Degeneration is usually present in older aged people.

ETIOLOGY

Result of persistent, mild irritation in the teeth.

CLINICAL FEATURES

- Early stages—No symptoms.
- Later stages—Discoloration of tooth. No response of pulp to stimuli.

TYPES

- Calcific degeneration
 - Part of pulp tissue replaced by calcific material, i.e. formation of pulp stones and denticles
 - Calcific material has onion skin appearance, lies unattached within body of pulp
 - In another type, calcific material is attached to the wall of the pulp cavity called as diffuse calcification
- Atrophic degeneration
 - Observed in older people
 - Pulp tissue less sensitive than normal
- Fibrous degeneration
 - Replacement of cellular elements by fibrous connective tissue
 - Pulp has characteristic appearance of a leathery fiber
- Pulp artefacts
 - Vacuolization of odontoblasts was once thought to be a type of pulp degeneration characterized by empty spaces occupied by odontoblasts
 - It is an artefact caused by poor fixation of the tissue specimen
- Tumor metastasis
 - Rare
 - May occur due to direct local extension from the jaw.

PULP CALCIFICATIONS

- May be located in pulp chambers or in root canals
- No sex predilection
- May occur in any teeth in either of the dental arches
- Basically of two types:
 1. Discrete pulp stones (denticles, pulp nodules)
 2. Diffuse calcification.

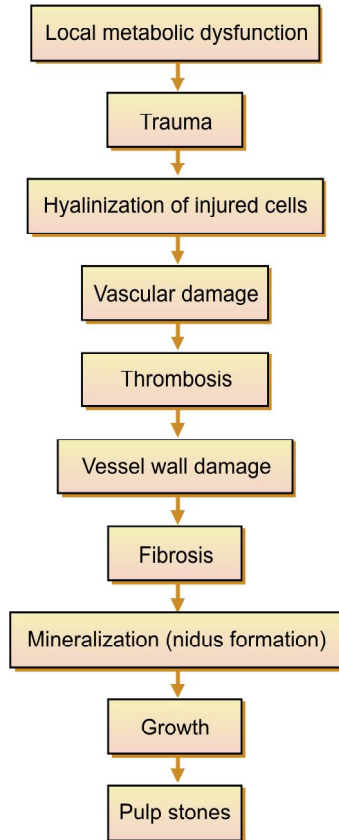
Sundell schematic presentation

FIGURE 3.17: Schematic representation of formation of pulp stones

ETIOLOGY

Refer Fig. 3.17.

DISCRETE PULP STONES

They are of following types:

- **True denticles**
 - Made of local masses of calcified tissue
 - Resemble dentin due to their tubular structure
 - More common in pulp chamber than root canals.

They are subdivided into two:

 1. Free denticle: Lying entirely within pulp tissue and is not attached to the dentinal wall (Fig. 3.18).
 2. Attached denticle: Continuous with dentinal wall.
- **False denticles**
 - Composed of localized mass of calcified material
 - Composed of concentric layers or lamellae deposited around a central nidus
 - Composed of cells surrounded by reticular fibers that calcify

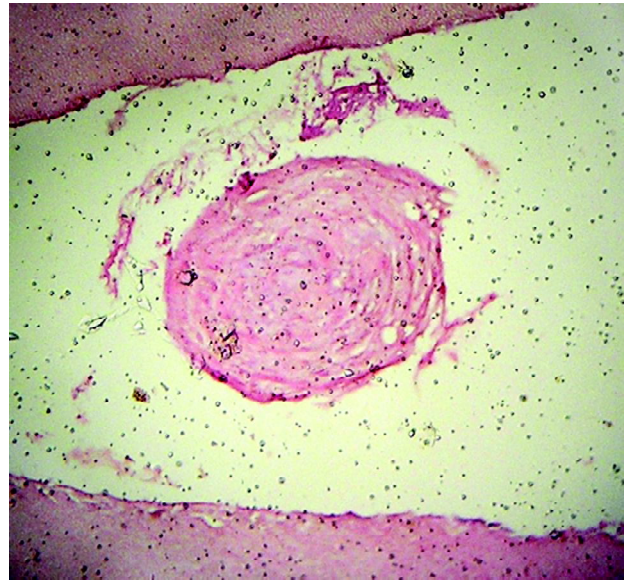


FIGURE 3.18: Free denticle within the pulp, lined by dentin

- They are larger than true denticles and mostly occupy pulp chamber
- They are also classified as free or attached.
- **Interstitial denticles**
 - After deposition of calcified material, a stage comes when this material is in apposition with the dentinal wall.
 - This material is then surrounded by secondary dentin and is then called as interstitial denticle.

DIFFUSE CALCIFICATION

- Also called calcific degeneration
- Amorphous unorganized linear strands or columns parallel with blood vessels and nerves of the pulp (Fig. 3.19).

RETICULAR ATROPHY OF PULP

- Degenerative or regressive change of pulp.
- Tooth is symptomless and responds normally to the vitality test.
- Presence of large vacuolated spaces in the pulp with reduction in number of cellular elements.
- Degeneration and disappearance of odontoblasts.

PULP NECROSIS

May be partial or complete.

ETIOLOGY

- Sequelae of inflammation
- May occur following trauma in which pulp is destroyed before an inflammatory reaction.

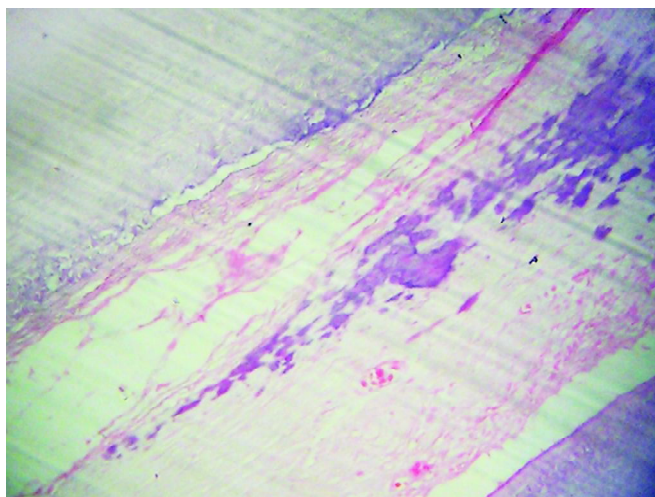


FIGURE 3.19: Diffuse calcification within the pulp, surrounded by dentin on both sides

TYPES

- **Coagulation necrosis:**
Soluble portion of tissue is precipitated or converted into solid material.
- **Liquefaction necrosis:**
Results when proteolytic enzymes convert the tissue into softened mass, liquid or amorphous debris.

CLINICAL FEATURES

- No painful symptoms.
- May cause swelling or distension of periapical tissue.
- Discoloration of tooth.
- Tooth with partial necrosis may respond to thermal changes owing to few vital nerve fibers.
- History of severe pain lasting from few minutes to few hours followed by cessation of pain.

HISTOPATHOLOGIC FEATURES

- Necrotic pulp tissue, cellular debris and microorganisms.
- Periapical tissue may be normal or there is slight inflammation.

Management

1. Complete debridement necessary.
2. Root canal therapy.

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Sequelae of Pulp Pathologies in Children

Shweta Dixit Chaudhary, Mayur Chaudhary

CHAPTER OVERVIEW

Introduction
Classification
Parulis
Acute alveolar abscess
Acute apical periodontitis
Acute exacerbation of chronic lesion
Chronic alveolar abscess
Granuloma
Apical periodontal cyst
External root resorption

Osteomyelitis:
Acute suppurative osteomyelitis
Infantile osteomyelitis
Chronic focal sclerosing osteomyelitis
Chronic osteomyelitis with proliferative periostitis
Cellulitis (phlegmon)
Ludwig's angina
Intracranial complication of dental infections:
Cavernous sinus thrombosis/thrombophlebitis
Focal infection

INTRODUCTION

The reaction of the pulp to initial insult has been discussed in the previous section. On persistence of the insult, the pulp may not be able to recuperate, leading to one of the sequelae of pulpal pathology which will be discussed in the present section.

CLASSIFICATION OF DISEASES OF PERIRADICULAR TISSUES

- WHO classification does not take into consideration the structural aspects of diseased tissues (Table 4.1).
- It is a histopathologic classification based on:
 - Distribution of inflammatory cells within the lesion,
 - The presence or absence of epithelial cells,
 - Whether the lesion has been transformed into a cyst, and
 - The relationship of the cyst cavity to the root canal of the affected tooth.
- Grossman, 1991, proposed a classification based on the clinical aspects of the diseased tissues (Table 4.2).

TABLE 4.1: WHO 1995.¹ Classification of diseases of periapical tissues

Code No.	Category
K04.4	Acute apical periodontitis
K04.5	Chronic apical periodontitis (Apical granuloma)
K04.6	Periapical abscess with sinus (Dentoalveolar abscess with sinus, Periodontal abscess of pulpal origin)
K04.60	Periapical abscess with sinus to maxillary antrum
K04.61	Periapical abscess with sinus to nasal cavity
K04.62	Periapical abscess with sinus to oral cavity
K04.63	Periapical abscess with sinus to skin
K04.7	Periapical abscess without sinus (Dental abscess without sinus, dentoalveolar abscess without sinus, periodontal abscess of pulpal origin without sinus)
K04.8	Radicular cyst (Apical periodontal cyst, periapical cyst)
K04.80	Apical and lateral cyst
K04.81	Residual cyst
K04.82	Inflammatory paradental cyst

ACUTE ALVEOLAR ABSCESS (FIG. 4.1)

An acute alveolar abscess is a localized collection of pus in the alveolar bone at the root apex of a tooth following death

TABLE 4.2: Grossman's classification, 1991, of diseases of periradicular tissues²

1. Acute periradicular disease
 - Acute alveolar abscess
 - Acute apical periodontitis
 - Vital
 - Nonvital
2. Chronic periradicular diseases with areas of rarefaction
 - Chronic alveolar abscess
 - Granuloma
 - Cyst
3. Condensing osteitis
4. External root resorption
5. Diseases of periradicular tissues of non-odontogenic origin

**FIGURE 4.1:** Acute alveolar abscess in deciduous molar

of the pulp with extension of the infection through the apical foramen into the periradicular tissues.

Also commonly known as acute abscess, acute apical abscess, acute dentoalveolar abscess, acute periapical abscess and acute radicular abscess.

ETIOPATHOGENESIS

- Trauma, mechanical irritation, chemical irritation
- Carious tooth leading to bacterial invasion with necrosis of the pulp leading to a periapical abscess
- Infection extends in the direction of least resistance, i.e. through apical foramen
- Contained pus may break through and a sinus tract opening in the labial or buccal mucosa, skin of patient's face, neck, antrum or nasal cavity may be seen
- At times, there is liquefaction of pus due to enzymes trypsin and cathepsin
- Point at which pus breaks in the mouth depends on the thickness of alveolar bone and the overlying soft tissues.

BACTERIOLOGY

- Mixed microflora is seen with approximately 32 percent anaerobes³
- Various species of streptococci, staphylococci, *Bacteroides melaninogenicus* have been seen
- Purulent discharge may be sterile with dead leukocytes and dead bacteria.

CLINICAL FEATURES

- Systemic reactions like fever, chills, malaise, headache, loss of sleep may be present
- Severe, throbbing pain in the region with localization of pain
- Swelling of the adjacent tissues
- Mobility of the involved tooth
- If left unattended, this may progress to osteitis, cellulitis or osteomyelitis
- Sinus opening may be seen on the labial or buccal mucosa with respect to the affected tooth, skin of patient's face, neck, antrum or nasal cavity
- Sinus opening usually seen through the labial alveolar plate in the maxillary arch
- Suppuration from the maxillary lateral incisor or from the palatal root of deciduous molars and permanent maxillary molars expresses palatally as the root of the maxillary lateral incisor and palatal roots of maxillary molars lie closer to the palatal plate of bone
- In the mandibular arch, suppuration usually expresses through the buccal alveolar plate
- May also occur through the lingual alveolar plate in the mandibular molars because of close proximity of the roots.

PARULIS

- At the intraoral opening of a sinus tract, often there is a mass of subacutely inflamed granulation tissue known as parulis (gumboil)
- No symptoms of pain may be present if a non-vital tooth is associated with parulis making it difficult to determine the causative tooth
- Gutta-percha point insertion into the tract during radiographic examination can aid in the diagnosis.

RADIOGRAPHIC FEATURES

- As lesion is present for short period of time and confined to medullary bone, no destruction of alveolar bone seen
- Slight widening of periodontal ligament membrane is seen
- In long standing cases, periapical rarefaction will be evident.

BACTERIOLOGY

- Microorganisms mostly involved are streptococci and staphylococci.
- Sundqvist used anaerobic culture methods and detected *Bacteroides melaninogenicus* in cultures.⁴

HISTOPATHOLOGIC FEATURES

- Area of suppuration composed of :
 - Central area of disintegrating polymorphonuclear leukocytes (Fig. 4.2)
 - Dilatation of blood vessels
 - Tissue around area of suppuration contains serous exudate.

Management

1. Immediate establishment of drainage.
2. Pulpectomy or extraction as indicated of the concerned tooth.
3. Control of systemic reactions.

ACUTE APICAL PERIODONTITIS

Acute apical periodontitis is a painful inflammation of the periodontium as a result of trauma, irritation or infection through the root canal, regardless of whether the pulp is vital or non-vital.

Acute apical periodontitis is said to be primary when inflammation is of short duration, initiated within healthy periodontium in response to irritants, and considered secondary when acute response occurs in already existing chronic apical periodontitis lesion (periapical flare-up, 'phoenix abscess').

ETIOLOGY

- In vital tooth due to:
 - Wedging of foreign object between teeth
 - Trauma (overcontoured restoration)
- In non-vital tooth due to:
 - Diffusion of bacteria and noxious products from inflamed or necrotic pulp.
 - Iatrogenic cause: Forcing of bacteria or of irritating medicaments through apical foramen, over-instrumentation during cleaning and shaping of root canal, extension of root canal material through apical foramen.

CLINICAL FEATURES

- Patient gives previous history of pulpitis.
- Tooth slightly elevated from the socket (due to edema).
- Patient feels tenderness while biting.

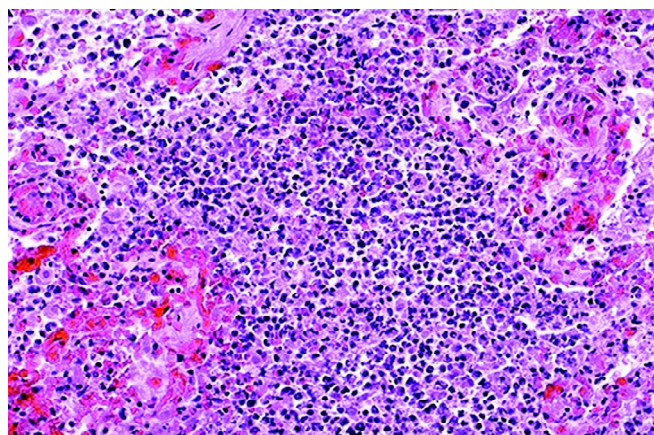


FIGURE 4.2: Acute alveolar abscess showing numerous polymorphonuclear leukocytes and dilated blood vessels

- External pressure on tooth forces edema fluid against already sensitized nerve endings and results in pain.

RADIOGRAPHIC FEATURES

- In vital tooth:
 - Little variation ranging from normal to widening of periodontal ligament.
- In non-vital tooth:
 - Changes range from widening of periodontal ligament space and resorption of lamina dura due to destruction of apical bone resulting in well-demarcated radiolucency.

HISTOPATHOLOGIC FEATURES

- Dilated blood vessels.
- Presence of distinct polymorphonuclear leukocytes (Fig. 4.3).
- Accumulation of serous exudate.
- Distension of periodontal ligament.
- Severe irritation leads to activation of osteoclasts and resorption of periapical bone.

Management

1. Determining the cause and relieving of symptoms.
2. Conservative treatment by removing the cause of periodontitis in a vital tooth.
3. Pulpectomy while avoiding the use of irritating medicaments, overinstrumentation and overobturation.

ACUTE EXACERBATION OF CHRONIC LESION

Acute exacerbation of a chronic lesion is also known as **phoenix abscess** after the bird phoenix which had arisen from the ashes according to Greek mythology.

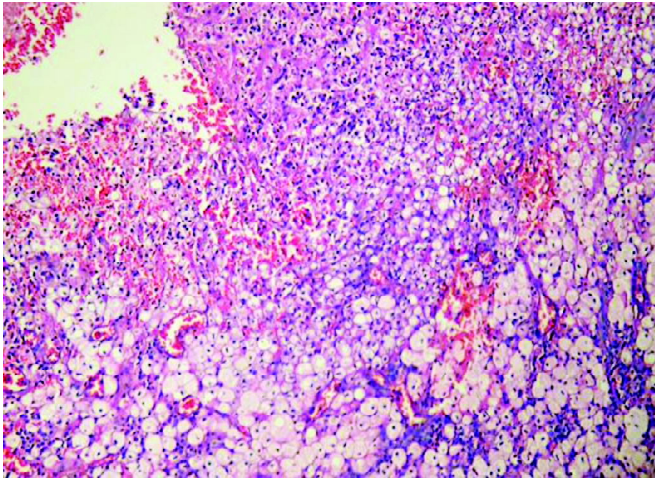


FIGURE 4.3: Acute apical periodontitis showing dilated blood vessels and presence of polymorphonuclear leukocytes

This condition is an acute inflammatory reaction superimposed on an existing chronic lesion, such as cyst or granuloma.

ETIOLOGY

- Influx of necrotic products from diseased pulp.
- Bacteria and their toxins.
- Reactivation of dormant lesions such as granulomas and cysts.

CLINICAL FEATURES

- Tooth tender on percussion.
- Tooth elevated from the socket.
- Mucosa over radicular area swollen and red.

RADIOGRAPHIC FEATURES

Well-defined periradicular radiolucent lesion (Fig. 4.4).

BACTERIOLOGY

Microorganisms are generally not seen in this lesion, if present, are transient microorganisms.⁵

HISTOPATHOLOGIC FEATURES

- Areas of liquefaction necrosis with disintegrating polymorphonuclear leukocytes and cellular debris
- Areas of necrosis are surrounded by infiltration of macrophages and lymphocytes (Fig. 4.5).

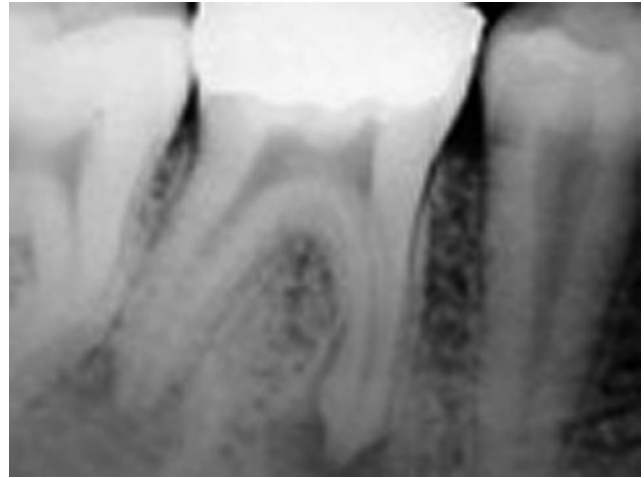


FIGURE 4.4: Phoenix abscess showing well-defined periradicular radiolucency

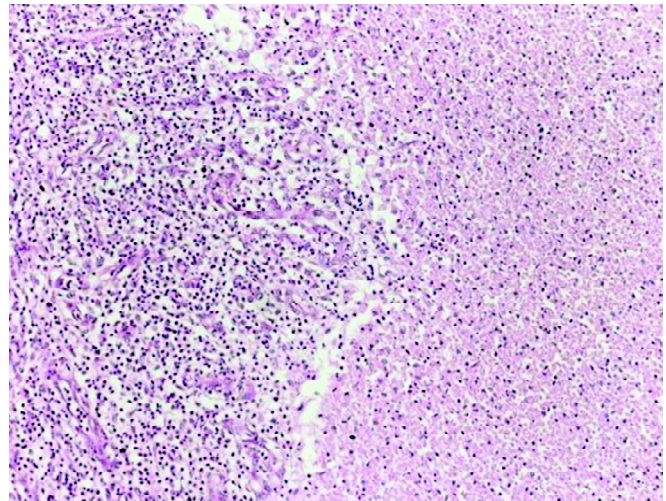


FIGURE 4.5: Phoenix abscess showing necrotic area with numerous inflammatory cells infiltrate

Management

1. Establishment of drainage.
2. Control of systemic reactions.
3. Pulpectomy.

It is appropriate at this stage to discuss why intratreatment pain occurs:

Intratreatment pain may be due to the following factors:

- Apical periodontitis secondary to treatment
 - Throbbing, gnawing and/or pounding pain.
 - Cause is frequently overinstrumentation causing pushing of necrotic debris and microbial by-products as well as microbes through the apical foramen.

- May be due to overmedication, overirrigation causing irritation of the periapical tissues.
- Incomplete removal of pulp tissue
 - Pain returns, after removal of coronal tissue only, during an emergency treatment.
- Recrudescence of chronic apical periodontitis
 - Also called **phoenix abscess**
 - Exact reason not known
 - May be due to change in environment
 - May be due to organisms or at times may occur in absence of organisms.

CHRONIC ALVEOLAR ABSCESS

Chronic alveolar abscess is also known as chronic suppurative apical periodontitis. A chronic alveolar abscess is a long-standing, low-grade infection of the periradicular alveolar bone.

ETIOLOGY

- Sequela of death of the pulp.
- Resulting from pre-existing acute alveolar abscess.

CLINICAL FEATURES

- History of sudden, sharp pain that subsided and did not recur or history of a traumatic injury
- Generally asymptomatic
- Presence of sinus tract
- Sometimes healing of sinus tract may occur with elevation of mucosa and “gumboil” (Fig. 4.6)
- Sinus tract in lower anterior teeth opens near symphysis
- In lower molars, it opens along the lower border of mandible
- The purulent material in deciduous teeth may pass into the gingival sulcus giving the impression of a periodontal pocket.

RADIOGRAPHIC FEATURES

- Diffuse area of bone rarefaction
- Widening of periodontal ligament space.

BACTERIOLOGY

- **Block RM et al 1976**, examined 230 periapical specimens and found that bacteria were infrequently present⁶
- Bacteria mostly involved are alpha-hemolytic streptococci and obligate anaerobes.

HISTOPATHOLOGIC FEATURES

- Toxic products diffuse through apical foramen leading to detachment of periodontal ligament fibers at the root apex
- Polymorphonuclear leukocytes are seen at the center of the lesion (Fig. 4.7).



FIGURE 4.6: Gumboil

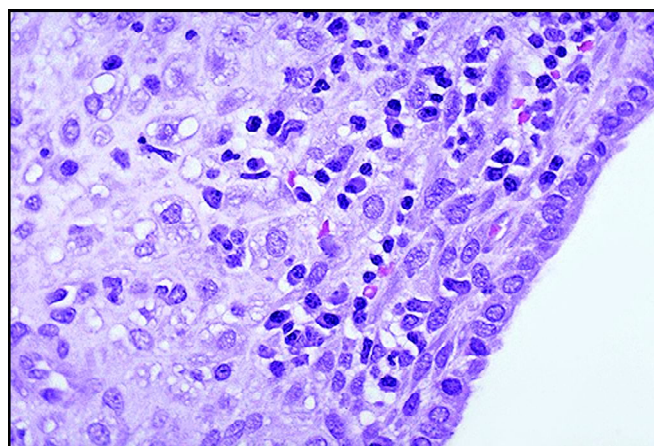


FIGURE 4.7: Chronic alveolar abscess showing a mixture of polymorphonuclear leukocytes, lymphocytes and plasma cells

- Lymphocytes and plasma cells are seen at the periphery of the lesion
- Fibroblasts may start to form a capsule at the periphery
- Sinus tract generally lined by granulation tissue
- Harrison JW, Larson WJ, 1976, found that 1 in 10 sinus tracts were lined by epithelium⁷
- Grossman, however, examined tissue in the tract as well as adjacent to the tract and found no evidence of epithelial lining of the tract.⁵

Management

1. Elimination of the infection of the root canal by pulpectomy, thorough debridement and irrigation of the root canals.
2. Sinus tract heals by granulation tissue formation.
3. If healing is delayed, thorough curettage of the tract is prescribed.

GRANULOMA

Granuloma may also be referred to as chronic apical periodontitis. A dental granuloma is a growth of granulomatous tissue continuous with the periodontal ligament resulting from death of the pulp and diffusion of bacteria and bacterial toxins from the root canal into the surrounding periradicular tissues through the apical and lateral foramina.

The term is a misnomer as its tissue is principally granulomatous comprising mostly of chronic inflammatory cell infiltrate in the fibrous connective tissue stroma of the granulation tissue.

ETIOLOGY

- Death of pulp followed by mild irritation or infection of periapical tissue
- In some cases, it is preceded by chronic alveolar abscess
- Stern, 1979, demonstrated that a granuloma is a cell-mediated response to pulpal bacterial products.⁸

CLINICAL FEATURES

- Nobuhara and del Rio showed that 59.3 percent of the periradicular lesions were granulomas, 22 percent cysts, 12 percent apical scars and 6.7 percent other pathoses⁹
- Involved tooth usually non-vital
- May be slightly tender on percussion
- Mild pain on biting or chewing
- In some cases, the tooth is elongated into its socket.

BACTERIOLOGY

- Post-extraction cultures were done by many authors and they found the specimen to be positive, possibly due to contamination of the specimen
- Burket L, 1938, found that a pre-extraction culture of bacteria through the root canal or alveolar plate showed the presence of *Streptococcus viridans*, *Streptococcus hemolyticus*, non-hemolytic streptococci, *Staphylococcus aureus*, *Staphylococcus albus*, *E. coli*, pneumococci.¹⁰

HISTOPATHOLOGIC FEATURES

- Granulomatous tissue replaces alveolar bone and periodontal ligament
- Rich vascular network, fibroblasts derived from periodontal ligament
- The new capillaries formed are lined by swollen endothelial cells
- Moderate infiltration of chronic inflammatory cell infiltrate mainly composed of lymphocytes and plasma cells (Fig. 4.8)
- Athanassiades and Spears,¹¹ Page and his associates¹² stated that immune granulomas show more lymphocytes and

plasma cells, while non-immune granulomas show more macrophages and giant cells

- When numerous plasma cells are present, scattered eosinophilic globules of gamma globulin called **Russel bodies** may be seen
- Clusters of light basophilic particles also may be present in association with plasmacytic infiltrate called **Pyronine bodies**
- Researchers have found a vast majority of lymphocytes in a granuloma but surprisingly, no immunoglobulin production was seen
- Non-B lymphocytes of T-cell origin are seen making the lesion an expression of delayed hypersensitivity
- T-cell activity results in expression of cytotoxic lymphokines, collagenase and mostly Osteoclast Activating Factor (OAF) resulting in resorption of bone
- Macrophages and foreign body giant cells may also be present
- Adams DO, 1976, stated that compared with granulomatous inflammation, banal chronic inflammation is a diffuse heterogeneous collection of cells, usually dominated by mononuclear cells other than macrophages, i.e. it lacks organization¹³
- In some granulomas, a large number of phagocytes ingest lipid material and are called as foam cells.
- Deposition of cholesterol as well as hemosiderin is often present
- Cholesterol crystals appear microscopically as needle-like spaces or clefts owing to dissolving of cholesterol during processing of tissues
- Connective tissue activity is prominent at the periphery of the lesion
- Condensation of bundles of collagen fibers is seen.

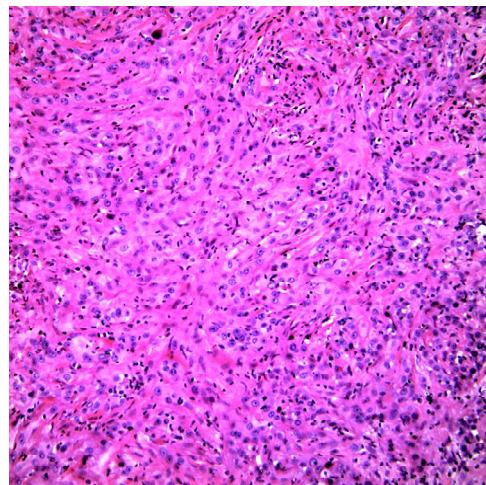


FIGURE 4.8: Periapical granuloma showing moderate infiltration of chronic inflammatory cell infiltrate

- Slow expansion of soft tissue mass leads to formation of continuous capsule and separates granulation tissue from the bone
- Another important feature is the presence of epithelium, which is mostly derived from epithelial cell rests of Malassez
- In some instances, it arises from:
 - Respiratory epithelium of the maxillary sinus in cases where lesion has perforated the sinus wall
 - Oral epithelium growing in through a fistulous tract
 - Oral epithelium perforating apically from a periodontal pocket, or bifurcation or trifurcation involvement by periodontal disease also with apical perforation.
- In early periapical granulomas, epithelium is confined to the immediate vicinity of periodontal ligament
- Later, it may proliferate by inflammatory stimuli and wall off the irritants coming into the periapical region through the apical foramen
- The epithelium forms sheets and anastomosing cords which are mainly responsible for formation of periodontal cyst
- Dunlap CL and Barker BF, 1977, coined the term **giant cell hyaline angiopathy** for periapical granuloma¹⁴
- It consists of inflammatory cell infiltrate, collection of foreign body giant cells and ringlike structures called **Rushton bodies** (eosinophilic material resembling hyalinized collagen).

FOREIGN BODY REACTIONS

Oral Pulse Granuloma

- It denotes a foreign body reaction to particles of vegetable food materials; e.g.: leguminous seeds that get lodged in oral tissues
- King,¹⁵ 1978, and Mincer HH et al,¹⁶ 1979, coined the term **pulse granuloma**
- Also referred to as giant cell hyaline angiopathy, vegetable granuloma and food induced granuloma
- Head MA, 1956, has reported pulse granuloma in lungs,¹⁷ Sherman FE, Moran TJ, 1954, have reported it in stomach walls and peritoneal cavities¹⁸
- Associated with teeth grossly damaged by caries and history of endodontic therapy
- Characterized by presence of intensely iodine and PAS positive hyaline rings or bodies, surrounded by giant cells and inflammatory cells
- Knoblich R, 1969, identified granuloma inducing agents to be cellulose, antigenic proteins and mitogenic phyto-hemagglutinins¹⁹
- Simon JHS, 1982, stated that vegetable food materials reach the periapex via root canals of teeth exposed to oral cavity, by trauma, carious damage or endodontic procedures²⁰

- Chen SY et al 1981, by immunoperoxidase procedure identified hyaline bodies as endogenous in origin.²¹

Management

1. Resolution of inflammation by removal of cause.
2. Pulpectomy.
3. If not responding to treatment, extraction.

Cellulose Granuloma

- White EW, 1968, reported that particles of predominantly cellulose containing material used in endodontic practice, medicated cotton wool for apical seal, endodontic paper points for microbial sampling and drying of root canals may get dislodged at the periapex.²²
- Sedgley CM, Messer H, 1993, stated that these particles, when not degraded by body cells, result in a foreign body reaction.²³

Gutta-percha

- Gutta-percha is a root canal sealant used for obturation of the root canal during endodontic therapy
- Gutta-percha cones get contaminated with tissue irritating substances leading to a foreign body reaction
- Nair PNR et al 1990, stated that the most striking feature is the presence of multinucleated giant cells and birefringent inclusion bodies²⁴
- Energy dispersive x-ray microanalysis demonstrated the presence of magnesium and silicon in inclusion bodies.

Other Foreign Materials

- Amalgam
- Endodontic sealants
- Calcium salts derived from periapically extruded calcium hydroxide.

APICAL PERIODONTAL CYST

Apical periodontal cyst is a slowly growing epithelial sac at the apex of a tooth that lines a pathologic cavity in the alveolar bone. It is also called as radicular cyst, periapical cyst and root end cyst.

ETIOLOGY

- Physical, chemical or bacterial injury resulting in death of the pulp followed by stimulation of epithelial cell rests of Malassez.
- In some instances, it arises from:
 - Respiratory epithelium of the maxillary sinus in cases where lesion has perforated the sinus wall.

- Oral epithelium growing in through a fistulous tract.
- Oral epithelium perforating apically from a periodontal pocket, or bifurcation or trifurcation involvement by periodontal disease along with apical perforation.

PATHOGENESIS

- Initial reaction is proliferation of epithelial rests in periapical area involved by granuloma.
- Proliferation is induced by keratinocyte growth factor elaborated by periodontal stromal cells.
- Gao et al speculated that activated T-cells in periapical granuloma caused lymphokine production leading to proliferation of epithelial cell rests of Malassez. Altered differentiation of these cell rests leads to cyst formation.²⁵
- This epithelial proliferation displays an irregular pattern.
- Basal cell layer of epithelium proliferates resulting in the central portion of the mass being separated from nutrition.
- Degeneration, necrosis and liquefaction of the central mass of cells occur.
- Thus, an epithelium-lined cavity filled with fluid is formed called as an apical periodontal cyst.
- The cyst increases in size by osmosis, fibrinolysis and continued epithelial proliferation.

THEORIES OF CYST FORMATION

- Nutritional deficiency theory
- Abscess theory
- Osmotic pressure theory
- Immune mediated theory.

Nutritional Deficiency Theory

- Central cells of epithelial strands removed from their source of nutrition result in necrosis and liquefactive degeneration
- Accumulating products attract neutrophils in the necrotic area
- Microcavities containing degenerating epithelial cells, infiltrating leukocytes and tissue exudate coalesce to form a cystic cavity lined by stratified squamous epithelium
- Torabinejad M, Walton RE stated that because there is no evidence of lack of blood supply and proliferating epithelium is usually invaginated by connective tissue, this theory is somewhat unsatisfactory.²⁶

Abscess Theory

- Proliferating epithelium surrounds an abscess formed by tissue necrosis and lysis because of the inherent nature of epithelial cells to cover exposed connective tissue surfaces.
- Torabinejad M, Walton RE stated that because of inherent differences between epithelial cell rests of Malassez and epithelial cells of skin, and because of numerous

discontinuities in the linings of apical cysts, this theory does not fully explain cyst formation.²⁶

Osmotic Pressure Theory

- This is the most widely accepted theory
- Skaug, 1974, 1977, reported that plasma protein exudate, hyaluronic acid, as well as products of cell breakdown contribute to the high osmotic pressure of the cystic fluid²⁷
- This osmotic pressure attracts more fluid and leads to cystic cavity formation and cyst expansion.

Immune Mediated Theory

- Development of cavities in proliferating epithelium is mediated by an immunologic reaction
- Immunocompetent cells in proliferating epithelium of periradicular lesion, presence of immunoglobulins in cystic fluids and discontinuity of epithelial lining in most of the apical cysts are seen
- Activated epithelial cell rests of Malassez can obtain antigenicity and become recognized as antigens.

CLINICAL FEATURES

- Majority of cases are symptomatic and may result in a prolonged, extremely troublesome and disconcerted course of events
- Commonly seen between 20 and 60 years but may occur at any age
- Most commonly involved teeth are the maxillary anteriors
- Associated teeth are either non-vital, show a carious lesion or may have undergone treatment
- Sometimes, it undergoes acute exacerbation leading to a phoenix abscess which may proceed to cellulitis or may form a draining fistula.

RADIOGRAPHIC FEATURES

- Localized radiolucent area surrounding the root of the involved tooth (Fig. 4.9)
- Occasionally, a thin radiopaque line around the periphery of radiolucent area is present indicating the reaction of bone to a slowly expanding mass
- Priebe WA et al 1954, decided on the clinical criteria for diagnosis, that an endodontically treated tooth if heals can be called as a granuloma, if not or if it takes a longer time to heal can be called as a cyst.²⁸

HISTOPATHOLOGIC FEATURES

- Similar to granuloma except for epithelium lined lumen.
- Epithelial lining is usually stratified squamous epithelium.
- In a newly formed cyst, epithelial thickness is uneven and often shows hyperplasia.



FIGURE 4.9: Periapical cyst showing localized radiolucent area surrounding the root of the tooth

- In an established cyst, epithelium has a regular appearance and a fairly even thickness.
- Gardener AF, 1969, reported the possibility of development of epithelial lining of this cyst into a carcinoma.²⁹
- Periapical true cyst is an apical inflammatory cyst with a distinct pathologic cavity, completely enclosed in an epithelial lining with no communication to root canal.
- Periapical pocket cyst is an apical inflammatory cyst containing a sac-like epithelium-lined cavity which is open and continuous with the root canal.
- Interesting and peculiar structures seen are the **Rushton bodies** in epithelium. They are tiny, linear or arc shaped bodies, associated with lining epithelium and are amorphous in reaction and brittle in nature.
- Allison RT, 1974, reported the frequency of occurrence of Rushton bodies between 2.6 and 9.5 percent.³⁰
- Sedano HO and Gorlin RJ, 1968, reported morphologic and histochemical similarity between these bodies and red blood cells.³¹ Rushton bodies arise from thrombus formation in small capillaries—a Rouleau phenomenon.
- Connective tissue made up of parallel bundles of compressed collagen fibers, numerous fibroblasts, blood vessels and inflammatory cell infiltrate consisting chiefly of lymphocytes and plasma cells makes up the wall of the cyst.
- Dystrophic calcification may also be seen.
- Contents of lumen vary from watery, straw colored, blood-tinged fluid to semisolid materials.
- Low concentration of proteins is seen in this cyst.

Cholesterol Crystals/Clefts

- Cholesterol stands for *Chloe-stereos* = “bile solid”.
- Cholesterol is a lipid of the steroid family. It is present in almost all tissues, abundant in myelin and other membrane rich tissues and cells.
- Cholesterol clefts are associated with multinucleated giant cells.
- In histopathologic sections, narrow, elongated clefts are seen because crystals dissolve in solvents during processing leaving behind clefts.
- Crystals are believed to be formed from cholesterol released by:
 - Disintegrating erythrocytes of stagnant blood vessels within the lesion.
 - Lymphocytes, plasma cells and macrophages disintegrate in chronic apical lesion.
 - Circulating plasma lipids.
- Cholesterol crystals erode the epithelium and are found in cystic lumen, such movement of crystals from epithelium to the cystic lumen is termed as **glacier-like** movement.
- Cystic fluid when held in sunlight shows a golden colored reflection, visible by naked eye. Such reflection is termed as **shimmering effect**.
- Accumulation of cholesterol crystals in body is called as cholesteatoma.
- Nair PNR et al 1990, coined the term **apical cholesteatoma** to distinguish deposition of cholesterol crystals in periapex from accumulation of cholesterol crystals in other body organs.²⁴
- Cholesterol crystals are hydrophobic in nature and thus need to be esterified to mobilize into lipid droplets and disperse into surrounding tissue fluids. Giant cells and macrophages have the property of esterification by incorporating phospholipids and lipoproteins into crystals. Thus, they are found around the cholesterol clefts.

Management

1. Nair PNR et al 1990, stated that “the presence of vast number of cholesterol crystals would be sufficient to sustain the lesion indefinitely”. So removal of such crystals might resolve the lesion.²⁴
2. Root canal therapy with apicectomy in permanent teeth; pulpectomy in deciduous teeth. Apicectomy is not recommended in deciduous teeth as the apices of these teeth are usually in a state of resorption.
3. Extraction of the involved tooth with curettage.

EXTERNAL ROOT RESORPTION

External root resorption is a lytic process occurring in the cementum or cementum and dentin of the roots of teeth. It is also called as odontoclasia.

ETIOLOGY

- Periradicular inflammation due to trauma.
- Excessive masticatory forces.
- Granuloma, cyst, central jaw tumors.
- Impaction of teeth.
- Iatrogenic causes like excessive orthodontic forces.
- Idiopathic causes.

CLINICAL FEATURES

- Tooth involved may be asymptomatic.
- It may be mobile.
- If resorption extends to the crown, it will give appearance of “pink tooth” seen in internal resorption.
- If tooth gets ankylosed, it will remain in infraocclusion (“submerged tooth”).

RADIOGRAPHIC FEATURES

- Concave or ragged areas on the root surface seen as a radiolucent area (Fig. 4.10).
- Blunting of apex.
- In case of ankylosis, no periodontal ligament space will be seen.
- In case of tumor, root resorption can be seen adjacent to the radiolucent area.

HISTOPATHOLOGIC FEATURES

- Varies from small areas of cementum resorption replaced by connective tissue or repaired by new cementum, to large areas of resorption replaced by osseous tissue, to “scooped out” areas of resorption replaced by inflammatory or neoplastic tissues. Multinucleated giant cells, i.e. odontoclasts are seen resorbing the root surface (Fig. 4.11).



FIGURE 4.10: External root resorption showing radiolucencies in the root and adjacent bone

Management

1. Management varies with the etiologic factor.
2. If pulpal disease extends into supporting tissues, root canal therapy is recommended.
3. If due to excessive orthodontic forces, reduction of forces is recommended.
4. Removal of impacted tooth should be done as soon as resorption due to the impacted tooth is discovered to avoid further increase in the crown root ratio.

OSTEOMYELITIS

Osteomyelitis is defined as inflammation of bone and its marrow contents. It is considered as an inflammatory condition of bone that usually begins as an infection of the medullary cavity, rapidly involves the Haversian system and quickly extends to the periosteum (Fig. 4.12).

CLASSIFICATION

- Suppurative osteomyelitis
 - Acute suppurative
 - Chronic suppurative
 - a. Primary—No acute phase preceding
 - b. Secondary—Follows acute phase
 - Infantile
- Non-Suppurative osteomyelitis
 - Diffuse sclerosing osteomyelitis
 - Focal sclerosing osteomyelitis (condensing osteitis)
 - Osteomyelitis with proliferative periostitis (Garre's osteomyelitis)
 - Osteoradionecrosis.

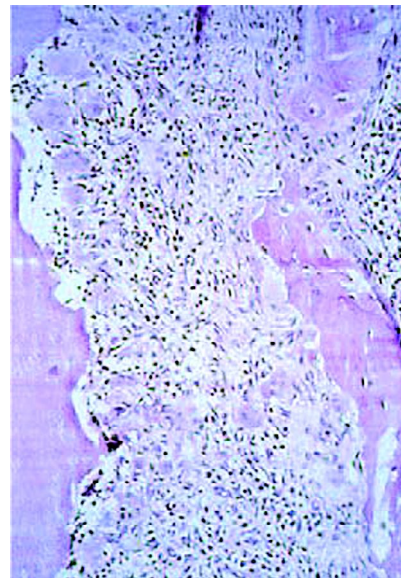


FIGURE 4.11: External root resorption showing multinucleated giant cells resorbing the root surface

Commonly seen in the pediatric population (first and second decades of life) are acute suppurative osteomyelitis, focal sclerosing osteomyelitis and osteomyelitis with proliferative periostitis.

PREDISPOSING FACTORS

- Trauma, jaw fractures
- Gunshot wounds
- Radiation damage
- Paget's disease
- Osteopetrosis
- Systemic conditions (malnutrition, uncontrolled diabetes mellitus, sickle cell anemia, acute leukemia and chronic alcoholism).

Acute Suppurative Osteomyelitis

- It is a serious sequela of periapical infection.
- Diffuse spread of infection throughout medullary spaces.
- Necrosis of variable amount of bone.
- Dental infection is a frequent cause.
- Usually of polymicrobial origin.
- Microorganisms involved are *Staphylococcus aureus*, *Staphylococcus albus*, streptococci, various anaerobes such as *Bacteroides*, *Porphyromonas* or *Prevotella*, *Eikenella corrodens*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Actinomyces* species.
- Also more common in patients of tuberculosis, syphilis, actinomycosis.

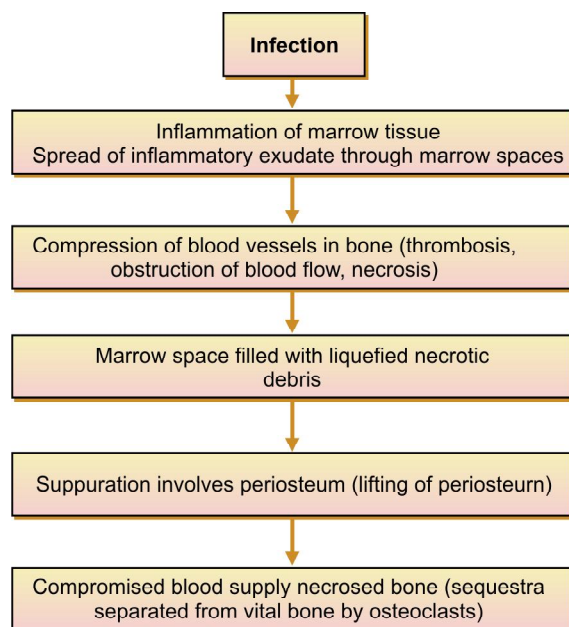


FIGURE 4.12: Mechanism of formation of osteomyelitis

Clinical Features

- Common in the first and second decades with slight male predilection
- May involve maxilla or mandible
- Usually localized in maxilla and diffuse and widespread in the mandible
- More common in posterior mandible in children and anterior maxilla in infants
- Neonatal maxillitis, occurs in infants and young children
- Occasionally caused by bacteremia
- Local oral infection following minor trauma
- Severe pain and trismus may be present
- Paraesthesia of lower lip occasionally may be present
- Elevation of temperature with regional lymphadenopathy
- Elevated white blood cell count
- Involved teeth become loose
- Exudation of pus may be seen usually near the lower border of mandible in children.

Radiographic Features

- Little radiographic evidence until two weeks
- Individual trabeculae become fuzzy and indistinct
- Ill-defined margins with moth eaten appearance.

HISTOPATHOLOGIC FEATURES

- Medullary spaces filled with inflammatory exudates, chiefly polymorphonuclear leukocytes, occasionally plasma cells and lymphocytes (Fig. 4.13).
- Osteoblasts bordering bony trabeculae are destroyed.
- Trabeculae may lose viability and undergo resorption with time.

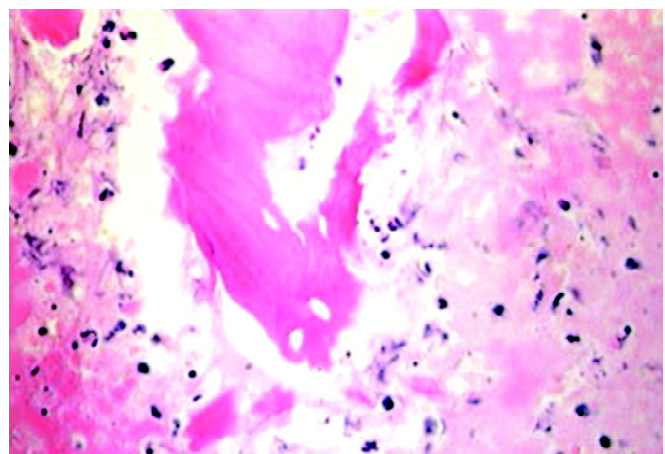


FIGURE 4.13: Acute suppurative osteomyelitis showing devitalized lamellar bone with scalloped edges and absence of stainable osteocytes and osteoblasts, edema and granulocytic infiltration of surrounding tissues

Management

1. Debridement of necrotic tissue.
2. Establishment of drainage through tooth or through the area where it is pointing.
3. Antibiotic therapy with culture and sensitivity testing along with antipyretics.
4. Adequate diet and avoidance of dehydration in children.
5. Sequestrectomy and saucerization of bone. Sequestrectomy has to be performed with utmost caution because of risk of damage to the underlying tooth bud.
6. Decortication of bone.
7. Immediate intervention is recommended.

Sequelae

Sequelae like periosteitis, soft tissue abscess, cellulitis and pathologic fracture are not uncommon.

Infantile Osteomyelitis

- Fortunately it is uncommon with risks of involvement of eye, extension to dural sinuses and potential for facial deformities.
- Usually occurs a few weeks after birth.
- Maxilla affected commonly.
- Before the advent of antibiotics, mortality rate was thought to be 30 percent, which has reduced drastically currently.
- Believed to occur by hematogenous route or perinatal trauma of oral mucosa from obstetrician's finger.

Clinical Features

- Malaise, hyperpyrexia, anorexia and dehydration.
- Inner and outer canthal swelling, palpebral edema, closure of eye and proptosis may result.
- Maxilla on the affected side is swollen both buccally and palatally.
- *Staphylococcus aureus* is the most common offending organism. Streptococci have also been found in cultures.

Management

1. Intravenous antibiotics and drainage of abscess.
2. Antipyretics for management of elevated temperature.
3. Proper diet and hydration. Dehydration is often the cause of fatality.
4. Sequestrectomy less preferred due to damage to tooth bud.

Chronic Focal Sclerosing Osteomyelitis

- Also called as condensing osteitis.
- It is an unusual reaction of healthy bone to infection where tissues react to infection by proliferation rather than destruction.
- Reaction to mild bacterial infection through a carious tooth or bacteria with low virulence.
- Infection acts as a stimulus rather than an irritant.

Clinical Features

- Most commonly seen in children and young adults chiefly in the first and second decades with no gender predilection.
- Most commonly involved tooth is a carious mandibular first molar.
- Patient complains of mild pain associated with an infected pulp.
- Sclerotic bone at the periapex may impede the eruption of succedaneous tooth.

Radiographic Features

- Well-circumscribed radiopaque mass of sclerotic bone surrounding and extending below the apex of one or both roots, with margins blending into the surrounding bone.
- Intact lamina dura.
- Widened periodontal ligament space.
- This is the most common periapical radiopacity.

Histopathologic Features

- Dense mass of bony trabeculae with little interstitial marrow tissue (Fig. 4.14).
- Empty lacunae are seen.

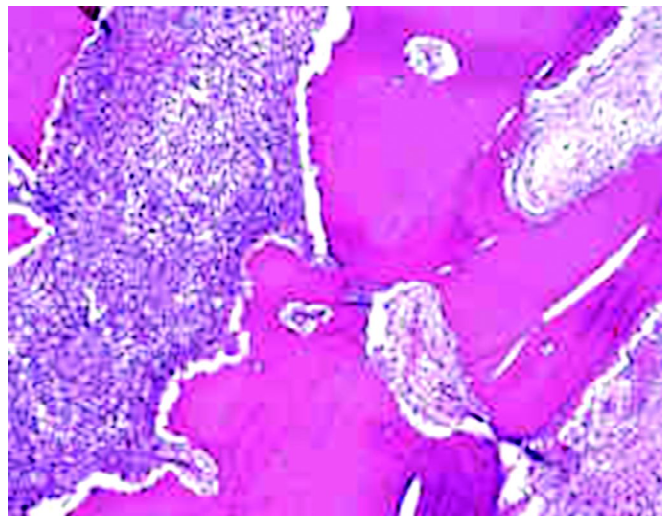


FIGURE 4.14: Dense mass of bony trabeculae with empty lacunae and little interstitial marrow tissue

- Interstitial soft tissue is fibrotic with an abundance of lymphocytes.
- Osteoblastic activity may have completely subsided by the time of microscopic study.

Management

1. No treatment of bony lesion is required.
2. Manage the odontogenic infection by pulpectomy, root canal therapy.
3. Lesion may regress after treatment or may result in a bony scar which may impede eruption of the succedaneous tooth.

Chronic Osteomyelitis with Proliferative Periostitis

- Also called as Garré's chronic non-suppurative sclerosing osteitis or periostitis ossificans.
- First described by Carl Garré in 1893.
- It is an irritation induced focal thickening of the periosteum and cortical bone of the tibia.

Clinical Features

- Occurs primarily in children, young adults and occasionally in older individuals with no gender predilection.
- Localized, hard, non-tender, unilateral bony swelling of lateral and inferior aspects of mandible.
- Mild tenderness may occasionally be present on palpation.
- Skin overlying the lesion appears normal.
- Occurs in bicuspid and molar region commonly.
- Maxilla is seldom affected.
- Patient complains of toothache and bony hard swelling on the outer surface of the jaw.

Radiographic Features

- Occlusal radiograph shows a focal overgrowth of bone on the outer surface of the cortex.
- Diffuse, poorly-defined mixed radiopaque and lucent expansile lesion.
- Duplication of cortical layer of bone ("onion skin appearance") (laminated appearance) is evident.
- Associated radiolucency with the involved tooth is seen.

Histopathologic Features

- Abundance of reactive osteoid tissue.
- Osteoblasts bordering many of the trabeculae are seen.
- Trabeculae are arranged perpendicular to the cortex.
- Fibrous connective tissue shows diffuse or patchy sprinkling of lymphocytes and plasma cells.

Management

1. Endodontic treatment or extraction of the involved tooth.
2. Antibiotic therapy.
3. Expanded bone usually remodels without surgical recontouring.

Spread of Infection

- An oral infection may originate in the dental pulp and extend through root canals into the periapical tissues. It may then become localized or extend diffusely.
- The routes by which infection can spread are:
 - Lymphatic system
 - Blood streams
 - Directly through the tissues.
- **Factors affecting the ability of infection to spread are:**
 - Type and virulence of organisms.
 - General health of the patient.
 - Anatomical site of initial infection which decides drainage of pus.
 - Immune status of the patient.
- Odontogenic infections often spread through natural pathways into potential tissue spaces situated between different planes of fascia.
- Infections into the various tissue spaces are known as **space infections**. Such infections in the vicinity of the jaw bones can be divided into two broad groups, namely those related to the maxilla and those related to the mandible.
- Examples of space infections are Ludwigs angina, cellulitis, canine fossa infection, palatal space infection, infra temporal space infection, submandibular space infection, etc.

CELLULITIS (PHLEGMON) (FIG. 4.15)

Cellulitis is a diffuse inflammation of soft tissues which is not circumscribed or confined to one area, but which in contradistinction to abscess, tends to spread through tissue spaces and along fascial planes.

This type of reaction occurs as a result of infection by microorganisms that produce significant amounts of streptokinase, hyaluronidase and fibrinolysins.

ETIOLOGY

- Streptococci are a common causative organism in case of cellulitis.
- Cellulitis of face and neck most commonly results from dental infection and infection following a dental extraction.

CLINICAL FEATURES

- Patient is moderately ill.
- Temperature is elevated.
- Leukocytosis.
- Painful swelling of soft tissues that is firm and brawny.
- Much of swelling is due to inflammatory edema.
- Regional lymphadenitis.



FIGURE 4.15: Periorbital cellulitis

HISTOPATHOLOGIC FEATURES

Shows diffuse exudation of polymorphonuclear leukocytes and occasional lymphocytosis.

Management

1. Broad spectrum antibiotics in combination with anti-anaerobic antibiotics.
2. Surgical intervention if necessary.

Ludwig's Angina

Ludwig's angina can be defined as severe cellulitis, beginning usually in the submaxillary space and secondarily involving sublingual and submental space as well.

CLINICAL FEATURES

- 2nd and 3rd molars are the primary sites acting as a source of infection.
- It appears as a rapidly developing board-like swelling of the floor of the mouth and consequent elevation of the tongue.
- Swelling is firm, painful and diffuse, showing no evidence of localization.
- Difficulty in breathing, eating and swallowing present.
- Patients usually have high fever, increased pulse rate, increased respiratory rate and moderate leukocytosis.

- In younger children, dehydration is quick to develop.
- Infection may spread to parapharyngeal spaces, to the carotid sheath or to the pterygopalatine fossa.
- Most of the cases are mixed infections.

Management

1. Antibiotic therapy.
2. Surgical drainage by stab incision.
3. Emergency tracheostomy to prevent suffocation.
4. Sedation to relax the associated muscles in spasm.

INTRACRANIAL COMPLICATION OF DENTAL INFECTIONS

- Haymaker has given a series of 28 fatal infections occurring after tooth extraction.³²
- The infection process may proceed along fascial planes to the base of the skull and then traverse the skull by one or more routes to spread into the intracranial cavity.

CAVERNOUS SINUS THROMBOSIS/ THROMBOPHLEBITIS

Cavernous sinus thrombosis occurs due to formation of thrombus in the cavernous sinus or its communicating branches.

Infection of head, face and intraoral structures above the maxilla are prone to cavernous sinus thrombosis.

ROUTES OF SPREAD OF INFECTION

1. *External route:* Facial and angular veins carry infection from the face and lip. It is a very rapid mode of spread of infection because these large veins directly lead to the cavernous sinus.
2. *Internal route:* Pterygoid plexus carries infection especially from maxillary and mandibular 3rd molar. It is much slower because infection has to pass through a small and twisted venous passage.

CLINICAL FEATURES

- Headache, nausea, vomiting, pain, chills and fever are present at initial stages.
- Exophthalmos with edema of eyelid and chemosis.
- Paralysis of external ocular muscle with impairment of vision and sometimes photophobia and lacrimation due to occlusion of ophthalmic vein.
- Complete paralysis of 3rd, 4th and 6th cranial nerve.
- Death may occur due to brain abscess and meningitis.

Management

1. Antibiotic therapy.
2. Drainage.
3. Anticoagulant therapy.

FOCAL INFECTION

Focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection.

Focus of infection is a circumscribed area of tissue which is infected with exogenous pathogenic microorganisms and is usually located near mucous or cutaneous surfaces.

SPREAD OF INFECTION

Two accepted mechanisms of spread of infection are:

1. Metastases of microorganisms from an infected focus by hematogenous or lymphogenous spread.
2. Toxins or toxic products may be carried through the blood or lymphatic channels from a focus to a distant site where they may incite a hypersensitive reaction in the tissues.

Oral foci of infection are generally:

- Infected periapical lesion.
- Teeth with infected root canals.
- Periodontal diseases with special reference to extraction or manipulation.
- According to Fish and MacLean, pumping action during extraction may force microorganisms from the gingival crevice into capillaries of gingiva and pulp.³³
- Evidence indicates that extraction of teeth and minor oral procedures produce transient bacteremia that persists for over 30 min.

SIGNIFICANCE OF ORAL FOCI OF INFECTION

Oral foci of infection may cause or aggravate many systemic diseases like:

1. Arthritis: It has been proven that failure of removal of oral foci results in aggravation of rheumatoid arthritis.
2. Valvular heart diseases: Symptoms of infective endocarditis are often seen after extraction of teeth.
3. Gastrointestinal diseases: Frequent swallowing of microorganisms may lead to many gastrointestinal diseases.
4. Ocular diseases
5. Skin diseases: Eczema and urticaria are related to oral infection.
6. Renal diseases.

Luckily, occurrence of metastatic infection from mouth to a distant bodily site is not very common.

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Gingival and Periodontal Diseases in Children

Shweta Dixit Chaudhary, Mayur Chaudhary

CHAPTER OVERVIEW

Introduction	Puberty gingivitis
Prevalence of gingivitis in children	Fibromatosis
Classification of periodontal diseases and conditions	Genetic form
Gingiva	Pharmacologically induced gingival overgrowth
Simple gingivitis	Scorbutic gingivitis
Gingivitis associated with poor oral hygiene (local irritants)	Periodontal diseases in children
Allergy and gingival inflammation	Early onset periodontitis
Acute gingival disease	Localized aggressive periodontitis
Herpes simplex virus (HSV) infection	Generalized aggressive periodontitis
Recurrent aphthous ulcer	Prepubertal periodontitis
Acute necrotizing ulcerative gingivitis	Localized early onset periodontitis (localized juvenile periodontitis)
Acute candidiasis	Papillon-Lefèvre syndrome
Acute bacterial infections	Cyclic neutropenia
Chronic nonspecific gingivitis	Gingival recession
Desquamative gingivitis	Abnormal frenum attachment
Conditioned gingival enlargement	

INTRODUCTION

McCall,¹ 1938, and Baer,² 1974, suggested a possible connection between incipient periodontal diseases in children and severe disease processes and subsequent loss of teeth found in adults. Periodontal disease has long been recognized in children, but due to its incipient nature, has not received the kind of attention commanded by dental caries. Children and adolescents can have any of the several forms of periodontitis as described in the proceedings of the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions. However, chronic periodontitis is more common in adults, while aggressive periodontitis may be more common in children and adolescents.³

PREVALENCE OF GINGIVITIS IN CHILDREN

V. Dhar *et al* used the Löe and Silness Index to score gingivitis and found a slightly higher prevalence in girls⁴ (Tables 5.1 and 5.2).

CLASSIFICATION OF PERIODONTAL DISEASES AND CONDITIONS

At the 1999 International Workshop for the classification of the periodontal diseases organized by the American Academy of Periodontology, the following classification was internationally accepted by common consensus on the opinion of the diseases and conditions affecting the periodontium³ (Table 5.3).

GINGIVA

The gingiva, as described by Löe, Listgarten and Terranova, 1990, is the part of the oral mucous membrane that covers the alveolar processes and the cervical portions of the teeth.⁵

The gingival tissues are normally light pink, though the color may be related to the complexion of the person, the thickness of the tissue and the degree of keratinization. The surface of the gingiva has a stippled appearance, varying from fine to coarsely grained. In the healthy adult, the marginal

TABLE 5.1: Epidemiologic studies of gingival diseases in children

Sr. No.	Year	Investigators	Group studied	No. of children	Age group	% affected by gingivitis
1.	1940	Marshal-Day and Tandon	Middle class children in Lahore	756	13	68
2.	1940	Marshal-Day	Fluoride endemic area in northern India	203	5-18	59.6
3.	1944	Marshal-Day	Boys in Kangra district	200	13	81
4.	1947	Marshal-Day and Shourie	Low to middle class male school children in Lahore	1054	9-17	99.4
5.	1947	Marshal-Day and Shourie	Girls of high socioeconomic level at Lahore	179	9-17	72.3
6.	1960	Greene	School boys in low economic area of India	1613	11-17	96.9
7.	1965	Dutta	Boys and girls in Calcutta	1424	6-12	89.8
8.	2007	Dhar V, Jain A, Van Dyke TE, Kohli A	Government school children of Udaipur district	1,587	5-14	84.37

TABLE 5.2: Prevalence of gingivitis in children

Sr. No.	Age group	Overall prevalence of gingivitis	Mild gingivitis	Moderate gingivitis	Severe gingivitis
1.	5-7 years	78.72%	64.89%	11.17%	2.66%
2.	8-10 years	85.01%	61.16%	19.08%	4.77%
3.	11-14 years	85.22%	53.45%	28.57%	3.2%

gingiva has a sharp, knifelike edge; during the period of eruption in a child, however, the gingivae are thicker and have rounded margins.

SIMPLE GINGIVITIS

Gingivitis refers to inflammation limited to the soft tissues that surround the teeth (Fig. 5.1).

Clinical Features

Usually, clinically detectable inflammatory changes of the gingiva begin in childhood and increase with age. The frequency of gingivitis peaks between the ages of 9 and 14 years, with a decline thereafter till the age of 17 years, after which a steady and slow increase in the prevalence of gingivitis is seen till the sixth decade of life. It may be diffuse or confined to the free gingival margins or the interdental papilla. Earliest signs of gingivitis include loss of stippling and bleeding on gentle probing.

Histopathologic Features

There are four stages, three of which are confined to the gingiva whereas, there occurs periodontal breakdown in the fourth stage.

TABLE 5.3: Classification of periodontal diseases and conditions

Gingival diseases:

- Plaque induced gingival diseases
- Nonplaque induced gingival diseases

Chronic periodontitis:

- Localized
- Generalized

Periodontitis as a manifestation of systemic diseases:

Necrotizing periodontal diseases:

- Necrotizing ulcerative gingivitis (NUG)
- Necrotizing ulcerative periodontitis (NUP)

Abscesses of the periodontium:

- Gingival abscess
- Periodontal abscess
- Pericoronal abscess

Periodontitis associated with endodontic lesions:

- Endodontic-periodontal lesion
- Periodontal endodontic lesion
- Combined lesion

Developmental or acquired deformities and conditions:

- Localized tooth-related factors that predispose to plaque induced gingival diseases or periodontitis
- Mucogingival deformities and conditions around teeth
- Mucogingival deformities and conditions on edentulous ridges
- Occlusal trauma

Stage I: Initial Lesion

The changes seen are:

- Dilatation of capillaries and venules causing increased blood flow in the area

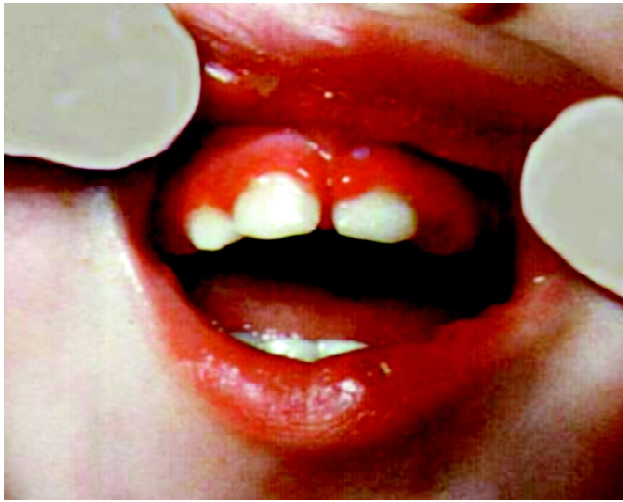


FIGURE 5.1: Gingivitis showing inflamed interdental gingiva

- Margination of neutrophils
- Increase in gingival crevicular fluid
- This stage may resolve or progress to the next stage with the appearance of lymphocytes and macrophages.

Stage II: Early Lesion

The changes seen are:

- Destruction of dentogingival and circular fibers
- Predominant cell type is lymphocyte
- Similar changes occur as seen in stage I, but with increased severity.

Stage III: Established Lesion

The changes seen are:

- Dilated blood vessels become engorged giving a bluish color to the gingiva
- Preponderance of plasma cells deep into the connective tissue
- Granular cell debris within widened intercellular space of junctional epithelium
- Elongated rete pegs of junctional epithelium
- Infiltrate of plasma cells, neutrophils, lymphocytes and mast cells
- Destruction of collagen fibers

Stage IV: Advanced Lesion

There occurs periodontal breakdown.

ERUPTION GINGIVITIS (FIG. 5.2)

It is a temporary type of gingivitis observed in children when teeth are erupting.

Clinical Features

- Associated with erupting teeth
- May be associated with difficult eruption



FIGURE 5.2: Eruption gingivitis showing inflammation in upper anterior region

- Usually subsides after the teeth emerge into the oral cavity
- Maximum incidence in the 6 to 7 year age group when the permanent teeth begin to erupt.

Etiopathogenesis

The gingivitis apparently occurs because the gingival margin receives no protection from the coronal contour of the tooth during the early stage of active eruption, and the continual impingement of food on the gingivae causes the inflammatory process. Local irritants like plaque, material alba and food debris often collect around and beneath the free tissue and cause development of the inflammatory process. The condition may be painful and may develop into a pericoronitis or a pericoronal abscess.

Radiographic Features

No radiographic changes are evident.

Histopathologic Features

Usually a mild inflammatory reaction is present showing an infiltrate of lymphocytes, plasma cells, neutrophils, mast cells and macrophages. Destruction of collagen is also evident.

Management

- No treatment for mild eruption gingivitis
- Improvement of oral hygiene
- Irrigation with counter-irritant such as peroxyol (Colgate-Palmolive Co, New York) in cases of painful pericoronitis
- Antibiotic therapy for pericoronitis accompanied by swelling and lymph node involvement.

GINGIVITIS ASSOCIATED WITH POOR ORAL HYGIENE (LOCAL IRRITANTS)

This type of gingival inflammation is associated with local factors like calculus, food impaction, faulty or irritating restorations or appliances, mouth breathing, tooth malposition, chemical and drug application, untreated carious lesions, etc.

Lindhe and Axelsson, 1973, examined the effects of various preventive measures on gingivitis in Swedish children. The plaque indices of the test group improved markedly over a 72 month period.⁶

Poulsen et al, 1976, demonstrated a reduction of gingival inflammation in Danish children seven years of age as a result of professional cleaning every two weeks for 72 months.⁷

Adequate mouth hygiene and cleanliness of teeth are related to frequency of brushing and the thoroughness with which bacterial plaque is removed from the teeth. Favorable occlusion and the chewing of coarse, detergent-type foods such as raw carrots, celery and apples have a beneficial effect on oral cleanliness.

Gingivitis associated with poor oral hygiene is usually classified as early, moderate, advanced.

Early gingivitis is quickly reversible and can be treated with good oral prophylaxis and through teaching good tooth brushing and flossing techniques to keep the teeth free of bacterial plaque.

ALLERGY AND GINGIVAL INFLAMMATION (FIG. 5.3)

Although it is difficult to assess the significance of gingival reaction during short allergic seasons, it has been suggested that patients with complex allergies who have symptoms for longer periods may be at higher risk for more significant adverse periodontal changes.



FIGURE 5.3: Gingival inflammation in upper and lower anterior region due to allergy

Matsson and Moller, 1990, studied the degree of seasonal variation of gingival inflammation in children with allergies to birch pollen. Their results indicated an enhanced gingival inflammatory reaction in the allergic children during the pollen seasons.⁸

ACUTE GINGIVAL DISEASE

HERPES SIMPLEX VIRUS INFECTION

Herpes simplex virus (HSV) infections are common vesicular eruptions of the skin and mucosa. They occur in two forms—systemic or primary and may be localized or secondary in nature. Both forms are self-limited but recurrences of secondary forms are common because the virus can be sequestered within ganglionic tissue in the latent stage.

Control rather than cure is the usual goal of treatment.

Pathogenesis (Fig. 5.4)

Physical contact with an infected individual is the typical route of HSV inoculation for a seronegative individual. The virus binds to the cell surface epithelium via heparan sulfate followed by the sequential activation of specific genes during the lytic phase of infection.

The incubation period after exposure ranges from several days to two weeks. In overt primary disease, primary gingivostomatitis or a vesiculoulcerative eruption occurs in the oral and perioral tissues. After resolution of primary herpetic gingivostomatitis, the virus migrates along the periaxon sheath of the trigeminal nerve to the trigeminal ganglion, where it is capable of remaining in a latent or sequestered state. No major histocompatibility (major histocompatibility complex) antigens are expressed, so there is no T-cell response during latency.

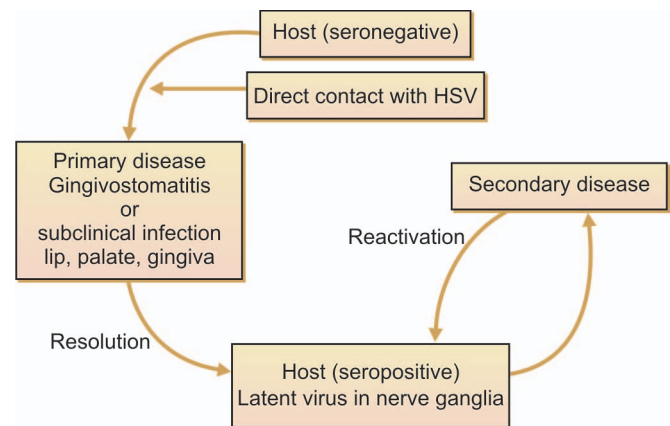


FIGURE 5.4: Pathogenesis of herpes simplex infection



FIGURE 5.5: Herpes simplex infection showing multiple ulcers around the face



FIGURE 5.6: Herpetic gingivostomatitis

Reactivation of virus may follow exposure to sunlight ("fever blisters"), exposure to cold ("cold sores"), trauma, stress or immunocompression.

Clinical Features

- The primary infection usually occurs in a child under six years of age.
- Most infections are subclinical (99%).
- Oral and perioral vesicles rupture forming ulcers (Fig. 5.5).
- Intra-oral lesions on any surface.
- Self-limited; symptomatic care.
- Immunocompromized patients have more severe disease
- The symptoms of the disease develop suddenly and include in addition to the fiery red gingival tissues, malaise, irritability, headache, and pain associated with the intake of food and liquids of acid contents.
- Characteristic oral finding is the presence of yellow or white liquid filled vesicles.
- In a few days the vesicles rupture and form painful ulcers, 1 to 3 mm in diameter, covered with the whitish-gray membrane and having a circumscribed area of inflammation (Fig. 5.6).

- The ulcers may be observed on any area of mucous membrane including buccal mucosa, tongue, lips, hard and soft palate and the tonsillar areas.
- Four-fold rise of serum antibodies to HSV-1.
- Lesion culture will be positive to HSV-1.

Histopathologic Features

- Intraepithelial vesicles containing exudates, inflammatory cells and characteristic virus-infected epithelial cells are seen
- Virus-infected keratinocytes contain one or more homogeneous, glassy nuclear inclusions
- HSV-1 cannot be differentiated from HSV-2 histologically.

Secondary Herpes Simplex

Reactivation of latent herpes simplex virus type 1 may occur due to triggering factors like exposure to sunlight, cold, trauma, stress or immunocompression. Lesions on the lip may also appear after dental treatment and may be related to irritation from rubber dam material or even routine daily procedures. Reactivation is common, although frequency decreases with aging. Prodromal symptoms like tingling and burning may be present. Sites affected are the same as in primary herpes simplex and the disease is self-limiting.

Management

1. Natural course of 10 to 14 days.
2. Basically symptomatic treatment is recommended.
3. Fluid and nutritional intake should be maintained.
4. Application of mild topical anesthetic such as 0.5 percent dyclonine hydrochloride (Dyclone) or lidocaine (Xylocaine Viscous) before meal time will temporarily relieve the pain and allow the child to take a soft diet.
5. Schaff, 1984, recommends a mixture of equal parts of diphenhydramine (Benadryl) elixir and kapectate as an alternative to the anesthetic. The diphenhydramine has mild analgesic and anti-inflammatory properties, whereas the kaolin-pectin compound coats the lesion.⁹
6. A vitamin supplement is indicated during the course of the disease as fruit juices will be irritating to the ulcerated area.
7. Zunt, 1999, suggested that the mainstay of definite therapy is regular doses of specific systemic antiviral medication combined with systemic analgesics.¹⁰
8. Acyclovir (Zovirax)—Five daily doses to equal 1000 mg per day for ten days. Available as capsules or suspension has been successfully used in infants and children.
9. Famciclovir (Famvir) and valacyclovir (Valtrex) are newer and possibly more potent antiviral agents but their use has not yet been adequately studied in pediatric populations.

10. Valacyclovir should not be prescribed for immuno-compromised patients.
11. Bed rest and isolation from other children in the family are recommended.
12. Sunscreen can prevent sun induced recurrences.
13. Most effective treatment for recurrences is the use of specific, systemic antiviral medications immediately after the prodromal symptoms of recurrence. The dosage remains the same while the course of treatment usually ends after five days.
14. A topical antiviral agent, penciclovir cream (Denavir) is available for extraoral lesions (not to be used intraorally), to be applied every two hours while awake for four days. It is not to be used in children younger than two years of age.
15. Another remedy for the infection is the amino acid lysine based on its antagonistic effect on amino acid arginine. L-Lysine monohydrochloride is available in capsule form or tablets containing 100 or 312 mg of L-Lysine. This therapy resulted in control of disease.
16. Avoidance of foods containing arginine, e.g. cereals, seeds, nuts and chocolate and selection of foods with adequate lysine, e.g. dairy products, yeast are recommended. This may explain the low incidence of herpes in infants before they are weaned from a predominantly milk diet.

RECURRENT APHTHOUS ULCER

Recurrent aphthous ulcers (RAU) also referred to as Recurrent aphthous stomatitis (RAS) or canker sore is an unfortunately common condition characterized by painful ulceration on the mucous membrane that occurs in school aged children and adults. Because of the similarity between this disease and Herpes simplex infection, with respect to precipitating factors leading to development of lesions, certain aspects of clinical appearance of lesions, duration of lesions, chronic recurrence and general failure of response to any form of therapy, the two diseases have been generally confused until only a short time ago.

Etiology

Numerous etiological factors have been suggested:

- Bacterial infection: Barile, 1963,¹¹ Graykowski, 1966,¹² have strongly implicated a pleomorphic, transitional L-form of an α -hemolytic *streptococcus*, *Streptococcus sanguis*, as the causative agent of the disease. Graykowski et al have also shown that patients with recurrent aphthous ulcers, when tested with a *streptococcus* vaccine, give a positive delayed type of hypersensitive skin reaction in contrast to patients with no history of aphthae, who give a less frequent and less severe response.
- Immunologic abnormalities: Lehner, 1969, suggested that RAU is a result of an autoimmune response of the oral

epithelium. He showed both IgG and IgM binding by epithelial cells of the spinous layer of oral mucosa in patients suffering from RAU using a fluorescent antibody technique.¹³

- Iron, vitamin B12, folic acid deficiency: There has been some evidence that nutritional deficiencies might be of some significance in the etiology of RAU. In patients with iron, vitamin B12, folic acid deficiency, a prompt response to replacement therapy suggested a direct action on oral mucosa, although, it has been reasonably postulated that the presence of a deficiency allows the expression of an unrelated underlying tendency to ulceration and that the deficiency itself does not play a primary role.

Precipitating Factors

A variety of factors have been repeatedly identified immediately preceding the outbreak of aphthous ulcers:

- Trauma: Self-inflicted bites, oral surgical procedures, tooth-brushing, dental injections and dental trauma.
- Endocrine conditions: Premenstrual, menstrual, postmenstrual, post-ovulation. Rarely occurs during menarche and menopause.
- Psychic factors: Acute psychologic problems associated with precipitation of attacks.
- Allergic factors: History of asthma, hay fever or food or drug allergies.

Clinical Features

The pediatric age group for RAU is in first and second decades of life. There is a female predilection. They occur mostly in non-keratinized mucosa, e.g. buccal and labial mucosa.

RAU has been classified on the basis of clinical appearance and the time taken for healing of an ulcer as:

Minor Aphthous Ulcers

- Recurrent painful ulcers
- Superficial
- Oval in appearance
- Less than 1cm in diameter
- Resolves in 7 to 10 days.

Major Aphthous Ulcers (Fig. 5.7)

- Multiple, deep ulcers
- Greater than 1 cm in diameter
- Resolve in 2 to 6 weeks.

Herpetiform Variant

- First described by Cooke in 1960.¹⁴
- Showers of multiple small ulcers.



FIGURE 5.7: Major apthae in labial vestibule

- May be confused with herpes simplex but Brook and Sapp, 1976, showed that there was no herpes simplex as seen by cytologic, microscopic, immunofluorescent and serologic techniques.¹⁵

Associated with Behçet's Syndrome

- Range in size from several millimeters to a centimeter in diameter
- Erythematous border
- Ulcer covered by a gray or yellow exudate.

Histopathologic Features

Hematoxylin and eosin stained biopsy sections of the lesional tissue shows a fibropurulent membrane covering an ulcerated area. There is break in the continuity of epithelium. Superficial colonies of microorganisms may be present in this membrane. Connective tissue stroma consists of intense inflammatory cell infiltrate mostly consisting of neutrophils and lymphocytes.

A characteristic change of elongated nuclei containing a linear bar of chromatin extending towards the nuclear membrane around aphthous ulcer taken by cytologic smear was reported by Wood and his associates, 1975.¹⁶ The cells showing such change were termed as **Antischkow cells**. They are not pathognomonic of this lesion and may also be seen in sickle cell disease, megaloblastic anemia, iron deficiency anemia, children receiving cancer chemotherapy and even in normal people.

Management

1. Management is primarily symptomatic as it is a self-limiting disease with uneventful healing with rarely a scar formation except in unusually large ulcers.
2. Topical application of tetracycline to the ulcers is often helpful in reducing the pain and shortening the course of the disease. Mouth rinses with a suspension containing tetracycline (250 mg/5 ml 4 times a day

for 5-7 days) is also useful, but the suspension should not be swallowed.

3. Chlorhexidine mouthwash may also help in alleviating the symptoms of RAU.
4. 0.1 percent triamcinolone acetonide (Leder cort ointment, Kenalog in Orabase) may be applied to the surface of the lesions before meals to facilitate intake of food. This is a potent topical steroid. Moderately potent steroids like glucocorticoid may be administered or mildly potent corticosteroids may also be administered.
5. Meiller et al 1991, have reported that the duration and the severity of the lesions can be reduced significantly by vigorous rinsing with an antimicrobial mouthwash (Listerine Antiseptic) twice daily.¹⁷
6. Aphthasol, a topical paste containing 5 percent amlexanox to be applied 4 times daily after meals and at bedtime till the ulcer heals, is effective in reducing pain and accelerating the healing of RAU ulcers.
7. Xylocaine/Lidocaine, silver nitrate, benadryl, camphor phenol may be applied topically to alleviate the symptoms of the ulcer.
8. Diet supplementation with vitamin B12, folic acid, iron and zinc sulphate has been advocated.
9. Immune enhancement with the help of levamisole or vaccine, are modalities that are being tried.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS

Acute necrotizing ulcerative gingivitis (ANUG), also called as "trench mouth", was described during World War I where this condition was prevalent amongst the allied troops staying in trenches for long duration.

Etiology

Reade, 1963, described a case of ulcerative gingivitis in a 15 month old infant and demonstrated *Treponema vincentii* and gram negative *fusiform bacilli*.¹⁸ It is generally an endogenous *fuso-spirochetal* infection caused by predisposing factors. Some investigators believe that this infection may be caused by vibrio and coccal forms. Many experiments were conducted to find out the etiological agent pertaining to this infection by various investigators. Mc Donald et al 1963, in their experiments concluded that *Bacteroides melaninogenicus* was the true causative agent of necrotizing ulcerative gingivitis.¹⁹ Goldhaber and Giddon, 1964, have published an excellent review of this disease.²⁰

PREDISPOSING FACTORS

- Psychological stress
- Immunosuppression
- Smoking
- Upper respiratory tract infection



FIGURE 5.8: Acute necrotizing ulcerative gingivitis involving upper and lower gingivae

- Local trauma
- Poor nutritional status
- Poor oral hygiene.

Clinical Features

- This inflammatory condition involves the free gingival margin, the crest of gingiva and the interdental papillae.
- Rarely the lesions spread to soft palate and tonsillar areas; in such instances, the condition is called 'Vincent's angina'.
- It occasionally occurs in children 6 to 12 years old, and is common in young adults.
- Characterized by development of painful hyperemic gingiva and sharply punched out crater-like erosions of the interdental papillae of sudden onset (Fig. 5.8).
- Bleeding on probing is seen.
- Ulcers become covered by a grayish-green necrotic pseudomembrane.
- Usually begins at a single isolated focus but tends to spread and may eventually involve all gingival margins.
- Fetid odor.
- Inability to eat due to gingival pain and bleeding.
- Nature of pain—Superficial 'pressure'.
- Headache, malaise, low grade fever.
- Excessive salivation with metallic taste to the saliva.
- Regional lymphadenopathy.
- In severe infection, systemic manifestations including leukocytosis, gastrointestinal disturbances, and tachycardia may be seen.
- Healing results in an area which is hollowed out due to destruction of the crests of the interdental papillae which retain debris and microorganisms and serve as an "incubation zone" where recurrence of ANUG may occur.

TABLE 5.4: Difference between ANUG and acute herpetic gingivostomatitis

Sr. No.	ANUG	Acute herpetic gingivostomatitis
1.	Most frequent in young adults in a mouth in which irritants and poor oral hygiene are present	Most frequent in pre-school children
2.	Develops over a longer period	Rapid onset
3.	Usually limited to the gingivae	Usually gingivae, lips and cheeks are involved
4.	Therapeutic trial cleaning will bring along a favorable response	No change in signs or symptoms seen after therapeutic trial cleaning
5.	Therapeutic trial antibiotics will reduce the acute symptoms	No change in signs or symptoms seen after therapeutic trial antibiotics

- Early stages of conditions like *Hand-Schüller-Christian* disease or *Letterer-Siwe* disease are associated with many of the symptoms of vincent infection.
- Differences between ANUG and acute herpetic gingivostomatitis are cited in Table. 5.4.

Histopathologic Features

Hematoxylin and eosin stained sections of the lesional tissue show an ulcerated stratified squamous epithelium replaced by thick fibrinous exudates. The connective tissue stroma shows an intense hyperemia and dense inflammatory infiltrate chiefly consisting of polymorphonuclear leukocytes. Since the histopathological picture is non-specific, the diagnosis is based purely on clinical examination.

Microscopic Smear Examination

Smear material from this disease shows fusiform bacilli and spirochetes. Other microorganisms observed are filamentous microorganisms, vibrios, cocci. Along with the microorganisms seen, there are desquamated epithelial cells and polymorphonuclear leukocytes. Generally major causative microorganisms responsible for producing ANUG are:

Fusiform Bacillus

- Elongated rod with tapered ends
- 5 to 14 microns in length
- 0.5 to 1 microns in diameter
- Gram-positive, nonmotile, anaerobic, occurs singly or in clusters.

Borrelia vincentii

- Gram-negative spirochete with 3 to 6 long, loose spirals
- 10 to 15 microns in length
- Motile, anaerobic.

The bacterial smear may be of value as an aid in diagnosis of ANUG. However, it has been suggested that the presence of microorganisms in the tissues is due to surgical artifact. Schaffer, 1953, using light microscopy failed to find bacteria penetrating vital tissues.²¹ Listgarten 1967, however, with the help of electron microscopic techniques, could identify spirochetes between viable epithelial cells.²²

Management

1. Subgingival curettage, debridement, use of mild oxidizing solutions (diluted hydrogen peroxide) will help in a dramatic improvement in the symptoms of the disease.
2. Antibiotic therapy is indicated for patients having extensive inflammation.
3. Improved oral hygiene, use of mild oxidizing mouth-rinses after every meal, twice daily chlorhexidine mouthrinses will aid in overcoming the infection.
4. Recontouring of gingiva (gingivoplasty) if required.

ACUTE CANDIDIASIS

Candida albicans is a common inhabitant of the oral cavity but may be responsible for the opportunistic infection of oral cavity following decline in host resistance. The word *candida* is of Latin origin meaning glowing white or glistening, because of the appearance of glistening colonies on culture media. It is a yeast-like fungus causing an infection termed **candidiasis**, also referred to as **thrush**, **candidosis**, **moniliasis**.

[*Monile (L) = necklace—large group of moulds/fungi called fruit moulds. Few pathogenic ones were later separated and classified as candida.*]

Candida occurs in three forms pseudohyphae, yeast and chlamydospore.

Frequently classified into two types:

1. *Mucocutaneous candidiasis* (oral or oropharyngeal, intestinal, esophageal, etc.)
2. *Systemic candidiasis* (involves eyes, kidneys and other visceral organs).

The most common forms in children are pseudomembranous and erythematous candidiasis.

ACUTE PSEUDOMEMBRANOUS CANDIDIASIS

Clinical Features

- Occurs mainly in debilitated or chronically ill individuals. Common in children receiving oncology treatment, during periods of severe immunosuppression and neutropenia.
- May occur in young children after antibiotic therapy.
- No gender predilection.
- Oral lesions are soft, white to yellow, slightly elevated, furry plaques occurring on buccal mucosa, tongue, gingiva, floor of mouth (Fig. 5.9).



FIGURE 5.9: Acute pseudomembranous candidiasis showing white, curd-like patches on tongue

- The plaques consist of masses of fungal hyphae with intermingled desquamated epithelium, keratin, fibrin, necrotic debris, leukocytes.
- The patches show a radial pattern of growth varying in size and shape.
- After removal of these white patches, there is bleeding of the underlying surface.
- Mild burning sensation is experienced.
- Neonatal candidiasis, occurs during passage through the vagina and erupts clinically during the first two weeks of life.
- Infants may have diaper rash.

ACUTE ATROPHIC CANDIDIASIS

- Lesions appear red or erythematous rather than white, thus, appearing pseudomembranous where membrane had been wiped off.
- Lehner, 1964, states that this is the only type of candidiasis which is painful.²³
- Usually involve the palate and dorsum of the tongue.
- Lesions are sometimes ulcerated and crusted.
- More common in children with a lip sucking habit, which may lead to spread of the infection to the adjacent perioral skin.
- Accumulation of saliva in deep folds of the corners of the mouth allows for the colonization of fungal and bacterial organisms (angular cheilitis).

HISTOPATHOLOGIC FEATURES

Oral smear may be prepared by macerating fragments of the plaque material with 20 percent potassium hydroxide and examined for the typical hyphae.

Periodic acid-schiff (PAS) stained section of the biopsy shows yeast cells and hyphae or mycelia in the superficial and

the deeper layers of the involved epithelium. Chlamydo spores are seldom seen in histological section.

DIAGNOSIS

A detailed description about diagnosis has been given in the chapter on Infectious diseases in children.

Management

1. Improved oral hygiene is of importance which includes control of caries, keeping pacifiers and appliances clean, replacing contaminated tooth brushes.
2. Topical antifungal agents like compounded clotrimazole suspension (10 mg/ml) and nystatin oral suspension (100,000 U per ml) may be swished for 2 min. and swallowed/expectorated four times daily for two weeks. The patient should not eat or drink for 30 minutes afterwards. Adolescents can use 1 to 2 pastilles (200,000 U) slowly dissolved in the mouth five times daily.
3. All antifungal agents formulated for topical use contain sweeteners which may promote caries if used for an extended period. Nystatin solution contains 30 to 50 percent of sucrose. Daily use of topical fluoride is recommended to reduce the caries potential.
4. Clotrimazole troches (10 mg) also very rich in sucrose can be used by slowly dissolving in mouth, one troch every 3 hours while awake (5 per day) for 14 days. The child must be of age and maturity to comprehend and follow instructions to use troch vehicle. Liver toxicity has been reported in patients using clotrimazole. Further clinical studies are required to establish the safety of drug in children less than 3 years.
5. Systemic antifungal drugs are advantageous when other topically delivered medications are administered concurrently. It is usually reserved for children either not tolerating or failing topical treatment or those at risk of systemic infections.
6. Systemic agents include clotrimazole 6 mg/kg every 12 to 24 hours for 5 to 7 days; adolescents can use a 200 mg loading dose and then 100 to 200 mg once a day for about a week.
7. Ketoconazole may also be used in children at 5 to 10 mg/kg every 12 to 24 hours and in adolescents 200 to 400 mg every 24 hours for 5 to 7 days. It is highly effective and has the advantage of good patient compliance. Fluconazole is generally preferred over ketoconazole which has a greater risk of associated hepatotoxicity. Itraconazole and voriconazole are two additional azoles with excellent activity against candida.
8. Common side effects with systemic use include nausea, vomiting, pruritis, skin rash, abdominal discomfort, headache, abnormal liver function test and drug induced hepatitis.

9. Chlorhexidine gluconate 0.12 percent can be used as antimicrobial rinse and is most useful for maintenance purposes.
10. Antifungal ointments and creams include nystatin, clotrimazole, myconazole and ketoconazole.
11. For chronic cases of angular cheilitis, Mycolog II is the best choice when applied to the corners of the mouth three times a day for five days.

ACUTE BACTERIAL INFECTIONS

Acute bacterial infections have been commonly known to affect the oral cavities of children although the exact epidemiology is still debatable. Acute streptococcal gingivitis has been reported causing painful, vivid, red gingivae that bleed easily. Ulceration of the gingivae, gingival abscesses and enlarged papillae have been observed. Diagnosis requires laboratory tests. Management usually consists of broad spectrum antibiotics, chlorhexidine and antimicrobial mouthwashes and improved oral hygiene.

This topic is dealt with in detail in the section on bacterial, viral and fungal infections.

CHRONIC NONSPECIFIC GINGIVITIS

It is a long standing condition common in the preteenage and teenage period. Dietary inadequacies have been pointed out by various researchers as one of the contributing factors. Presence of malocclusion, mouthbreathing, etc. also lead to an accumulation of local irritants. It usually occurs due to the presence of a chronic local irritant. May be localized or generalized. The local irritant variously results in gingival inflammation, enlargement and ulceration with fiery red gingivae and further leads to a conducive environment for accumulation of plaque and materia alba. Histopathological features are similar to gingivitis except more number of plasma cells and lymphocytes are present.

DESQUAMATIVE GINGIVITIS

This is a type of chronic nonspecific gingivitis. The term "desquamative gingivitis" is more of a clinical description and has also been referred to as *gingivosis*. The term chronic desquamative gingivitis was coined in 1932 by Prinz.²⁴

Etiology

The exact etiology has not been established but McCarthy et al 1960, have suggested the following etiological factors:²⁵

- Hormonal influences
- Certain dermatoses
- Abnormal responses to irritation
- Chronic infections
- Idiopathic.

Clinical Features

- Mainly in the teenage group
- Gingiva appears intensely, fiery red with a characteristic desquamation of the surface epithelium.
- There may be swelling and glossy appearance of the gingivae due to loss of stippling.
- Multiple vesicles and denuded areas may be seen. Nikolsky's sign is positive which indicates slipping or peeling of the tissue at the dermal-epidermal junction under slight lateral pressure
- Buccal mucosa may be involved at times.

HISTOPATHOLOGIC FEATURES

Histopathologic features depend upon the condition, i.e. either mucous membrane pemphigoid or lichenoid reaction. The overlying epithelium may be atrophic or with blunt rete ridges. The connective tissue stroma is fibrous with chronic inflammatory cell infiltrate mostly consisting of lymphocytes and plasma cells. Sometimes clefting may be seen below the basement membrane.

Management

1. Thorough oral prophylaxis.
2. Elimination of predisposing factors like malocclusion, overhanging restorations, gingival and periodontal defects which predispose to the accumulation of local irritants.
3. Correction of dietary inadequacies.
4. Evaluation of hormonal imbalance and correction of the same if required.
5. Doxycycline monohydrate 100 g daily for 4 to 11 weeks.
6. Topical corticosteroid such as triamcinolone 0.1 percent or fluocinone 0.05 percent applied daily.

CONDITIONED GINGIVAL ENLARGEMENT (FIG. 5.10)

PUBERTY GINGIVITIS

Gingivitis is common in children and adolescents, especially around puberty. It is believed to be related to an increase in steroidal hormone. Granulomatous changes of the gingivae similar to those occurring in pregnancy may be visible.

Clinical Features

- Peak prevalence is 10 years in girls and 13 years in boys.
- Crowded teeth and orthodontic appliances may be important contributors as they render difficulty in practicing oral hygiene measures.

- Mouth breathing could lead to chronically dehydrated gingivae in the maxillary labial area leading to localized gingivitis.
- Marginal gingival enlargement is seen characterized by prominent bulbous interproximal papillae far greater than gingival enlargements associated with local factors.
- Usually only the anterior segment of one arch affected. The lingual gingival tissue generally remains unaffected.
- A longitudinal study carried by Mombelli A et al 1990 on subgingival microbiota of children between age group 11 to 14 years had implicated *Capnocytophaga* species in initiation of pubertal gingivitis.²⁶

Histopathologic Features

The overlying epithelium may show blunt rete ridges. Connective tissue stroma is loose, edematous with chronic inflammatory cell infiltrate.

Management

1. Thorough oral prophylaxis.
2. Motivating towards better practice of home oral hygiene measures.
3. Removal of all local irritants, restoration of carious teeth, dietary prescriptions to ensure adequate nutritional status.
4. 500 mg ascorbic acid may be administered orally daily for approximately four weeks for improvement in gingival inflammation.
5. Surgical management involves gingivoplasty and removal of the thickened fibrotic marginal and interproximal tissue.
6. Maintenance of adequate oral hygiene ensures minimal recurrence rate.



FIGURE 5.10: Conditioned gingival enlargement showing prominent bulbous interproximal papillae

FIBROMATOSIS

Fibromatosis is a slow, progressive, diffuse, benign, fibrous enlargement of gingiva. Basically it has been shown to occur in two forms:

1. Genetic and
2. Pharmacologically induced.

Genetic Form

Hereditary gingival fibromatosis, the most common genetic form of this lesion has been reviewed by Zackin and Weisberger, 1961, who reported a family of 11 affected and 10 normal children. It usually occurs as an autosomal dominant trait.²⁷ It may also be idiopathic. **Hart et al, 1998**, have identified the first polymorphic marker for this condition in chromosome 2p21.²⁸ This rare type of gingivitis has been referred to as **elephantiasis gingivae**.

Clinical Features

- Gingival tissues appear normal at birth but begin to enlarge with eruption of primary teeth.
- More common in the first and second decades.
- No sex predilection is seen.
- Affects both the dentitions.
- Usually affects the attached gingiva and maxillary tuberosity.
- Diffuse, firm, smooth to stippled or nodular overgrowth of gingiva in one or both the arches (Fig. 5.11).
- Pale in color.
- Pain is not the feature unless the overgrowth covers the teeth completely and then gets traumatized during mastication.
- Mobility and displacement of the teeth may be evident sometimes because of resorption of bone caused by pressure induced by the overgrowth
- Tooth eruption may be impeded due to the excessive tissue.

Radiographic Features

Resorption of bone may be evident on orthopantomogram (OPG) as a result of pressure induced by the overgrowth.

Histopathologic Features

Zackin and Weisberger, 1961, described the features of gingival fibromatosis similar to gingival hyperplasia. The epithelium is hyperkeratotic with thickened and elongated rete pegs (Fig. 5.12). Connective tissue stroma is dense and fibrous, filled with collagen fibers and interspersed blood vessels and fibroblasts between them.

Picrosirius red staining followed by polarizing microscopy can selectively demonstrate collagen. Differences in polarization colors are caused by fiber thickness, as well as by packing of collagen. Examination of collagen fibers of known thickness by this method can serve as a procedure to



FIGURE 5.11: Gingival fibromatosis almost completely covering the teeth

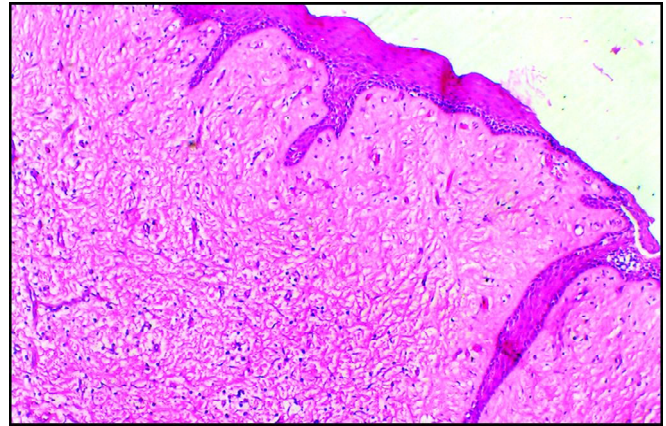


FIGURE 5.12: Hyperkeratotic epithelium with thickened and elongated rete pegs and connective tissue stroma is dense and fibrous

differentiate procollagens, intermediate and pathological collagen fibers. This has been shown to be of value in skin lesions, hyperplastic gingival and odontogenic tumors.

Syndromes Associated with Gingival Fibromatosis

- Byars-Jurkiewicz syndrome: Gingival fibromatosis, hypertrichosis, giant fibroadenomas of the breast and kyphosis
- Cross syndrome: Gingival fibromatosis, microphthalmia, mental retardation, athetosis and hypopigmentation
- Jones-Hartsfield syndrome: Gingival fibromatosis and sensorineural hearing loss
- Laband syndrome: Gingival fibromatosis; ear, nose, bone and nail defects; and hepatosplenomegaly
- Rutherford syndrome: Gingival fibromatosis and corneal dystrophy.

Management

1. Surgical removal of the hyperplastic tissue is recommended, however recurrences are common.
2. Good oral hygiene helps in delaying the recurrence of the growth.
3. Although the tissue usually appears pale and firm, the surgical procedure is accompanied by excessive hemorrhage. Hence, quadrant dentistry is recommended.
4. Apically positioned flap surgery and CO₂ laser evaporation have variously been used to reduce the gingival tissue.
5. When tooth eruption is impeded, surgical removal of the excessive tissue and exposure of the teeth are recommended.
6. Tooth extraction alone can cause the tissues to shrink almost to normal and recurrence can be prevented by this means.

Pharmacologically Induced Gingival Overgrowth

- Most commonly seen is phenytoin induced gingival overgrowth. Phenytoin was introduced by Merrit and Putnam in 1938.²⁹ Phenytoin (Dilantin diphenylhydantoin) is a major anticonvulsant agent used in the treatment of epilepsy. Kimball in 1939 first described varying degrees of gingival hyperplasia as a common side effect of phenytoin therapy.³⁰ Dilantin sodium induces gingival enlargements in 3 to 84.5 percent of patients receiving the drug. Other hydantoin known to induce gingival enlargements are ethosuximide and mephentermine. Gingival enlargements can occur after therapy with immunosuppressant cyclosporine or calcium channel blockers. Cyclosporine is used to control host rejection of transplanted organs and to manage autoimmune diseases. Cyclosporine has been reported to produce gingival enlargement in 30 percent of the patients receiving the drugs. Calcium channel blockers such as nifedipine and nitrendipine are cardiac drugs that are sometimes prescribed in children to control hypertension. Nifedipine induces gingival enlargements in 20 percent of the cases. There appears to be a genetic component to susceptibility to gingival enlargement.

Clinical Features

- Painless overgrowth, differs from chronic inflammatory enlargement in that it is fibrous, firm, dense, resilient, insensitive and pale pink often with little tendency to bleed.
- The enlargement first occurs in the interdental region and may appear lobular.
- It gradually spreads to the gingival margin.
- There is increased stippling which ultimately results in a roughened or pebbled surface with lobulations (Fig. 5.13).
- The overgrowth may sometimes cover the crown of entire teeth and interfere with eruption or occlusion.

- The severity of the enlargement is affected by adequacy of oral hygiene and the gingival concentration of the medication
- The most severe cases of gingival enlargement usually occur in mentally retarded patients in part due to poor oral hygiene.

Histopathologic Features

The epithelium is hyperkeratotic with thickened and elongated rete pegs. Connective tissue stroma is dense and fibrous, filled with collagen fibers and interspersed blood vessels and fibroblasts between them. Connective tissue stroma is dense and fibrous due to proliferation of fibroblast-like cells and decrease in the collagen degradation and chronic inflammatory cell infiltrate (Fig. 5.14).



FIGURE 5.13: Localized gingival fibromatosis in lower anteriors due to dilantin sodium intake

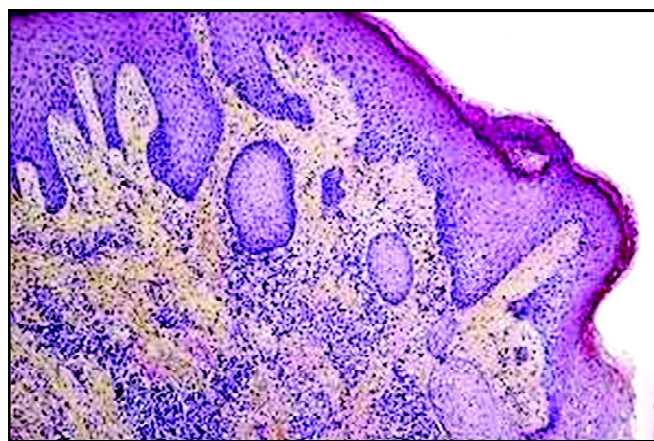


FIGURE 5.14: Localized gingival fibromatosis showing hyperplastic epithelium and chronic inflammatory cell infiltrate

Management

1. It is similar to gingival fibromatosis, although the tissue does not show the tendency to bleed.
2. Some regression of the enlargement may result if the use of the drug is discontinued.
3. If medication cannot be discontinued or changed, the enlargement can be surgically removed but it will recur.
4. Surgery is indicated when
 - Appearance of the gingiva is unacceptable to the patient.
 - Enlargement interferes with comfortable function.
 - Enlargement results in a periodontal pocket that cannot be maintained in a healthy state.
5. Post-operative discomfort after gingivectomy should be carefully weighed against potential benefits for patients who may not be able to give fully informed consent.

SCORBUTIC GINGIVITIS

This is gingivitis associated with vitamin C deficiency.

Clinical Features

- Severe pain and spontaneous hemorrhage.
- Only the marginal tissues and gingival papillae are involved.
- Although severe forms are rare in children, they may occur when a child is allergic to fruit juices.
- In mild forms, usually only inflammation and enlargement of the marginal gingival tissue and papillae occur.

HISTOPATHOLOGIC FEATURES

The overlying epithelium shows blunt rete ridges. The connective tissue stroma is loose, edematous with collagen degeneration and engorged capillaries. Chronic inflammatory cell infiltrate consisting mainly of plasma cells and lymphocytes may be seen.

Management

1. Dramatic response has been seen to a daily administration of 250 to 500 mg of ascorbic acid for four weeks.
2. Thorough oral prophylaxis alongwith improved oral hygiene measures will greatly improve the gingival condition.

PERIODONTAL DISEASES IN CHILDREN**EARLY ONSET PERIODONTITIS**

Recent terminology dictates the use of the term "Aggressive periodontitis" instead of former term of early onset

periodontitis. It is characterized by periodontal destruction that becomes clinically significant during adolescence or early adulthood. Ranney, 1993, classified the disease in localized and generalized form.³¹

1. Localized aggressive periodontitis is characterized by bone loss around the first molars and incisors.
2. Generalized aggressive periodontitis is characterized by a more widespread pattern of periodontal destruction.

Localized Aggressive Periodontitis (LAP)**Etiology**

- A strong association between LAP and a unique bacterial microbiota dominated by *actinobacillus actinomycetemcomitans* was reported by Newman, 1979³² and Nelson, 1999.³³
- Other microorganisms reported to be associated with LAP include *P. gingivalis*, *E. corrodens*, *C. rectus*, *F. nucleatum*, *Bacillus capillus*, *Capnocytophaga* species and *Spirochetes*.
- It has been found that the humoral immune response to *A.a.* is elevated in patients with LAP. Prevalence of *A.a.* is six times greater in LAP than in healthy patients.
- Prevalence of *A.a.* is greater in younger LAP patients who show a more destructive disease course than in the older ones. This could correlate with the disease activity.
- Prevalence of *A.a.* is less or absent at healthy site.
- *A.a.* has been known to be quite virulent as it produces a leukotoxin, collagenase, phosphatases, bone resorbing factors, as well as other factors important in invasion of host tissues, evasion of host defences, immunosuppression and destruction of periodontal tissues.
- A positive correlation has been found by Socransky and Haffajee, 1991, between the elimination of *A.a.* from subgingival flora and successful clinical treatment of LAP.³⁴
- Page, 1985, believes that transmission could be autosomal recessive while some others believe it to be an X-linked dominant mode of transmission.³⁵

Clinical Features

- The classic form of localized aggressive periodontitis was initially referred to as periodontosis and then as Localized juvenile periodontitis (LJP).
- Onset around the time of puberty in an otherwise healthy individual.
- Aggressive periodontal destruction localized almost exclusively to the incisors and first molars; less than 30 percent of sites are involved.
- Familial pattern of occurrence.
- Low incidence from 0.1 to 2.3 percent
- Females are affected more often than males; blacks are affected more than whites.

- Abnormality in phagocyte function.
- Self-arresting disease progression.
- One of the earliest signs is sudden symmetric pathologic drifting of teeth in a patient having a relatively good oral hygiene.
- The affected teeth become mobile very soon followed by pocket formation.
- Progression of bone loss is 3 to 5 times faster than adult periodontitis.
- Bone loss around the primary teeth can be an early finding in this disease.

Radiographic Features

- A localized vertical bone loss with widening of periodontal ligament (PDL) space.
- Arc shaped bone destruction starting from the distal margin of the second premolar and extending up to the mesial margin of the second molar.

Histopathologic Features

The features appear similar to chronic periodontitis. Soft tissue areas of periodontitis show a hyperplastic crevicular epithelium with exocytosis of acute inflammatory cells. Adjacent connective tissue shows chronic inflammatory cells consisting of lymphocytes and plasma cells.

Management

1. Early diagnosis aids in successful treatment.
2. Antibiotics can be provided against infective microorganisms- tetracycline sometimes in combination with metronidazole.
3. Surgical treatment includes raising a modified Widman flap, removal of the infected crevicular epithelium and debridement of root surfaces with a simultaneous 14 day course of 1g/day doxycycline hyclate.
4. DNA probe test for *A. a.* may be used for establishing the risk of aggressive periodontitis. Retesting after the completion of antibiotic therapy will detect the patients response to the treatment.
5. Keyes technique has been described by Rams, Keyes and Wright, 1985.³⁶ This technique involves:
 - Meticulous scaling and root planing of all teeth.
 - Concomitant irrigation to probing depth of saturated inorganic salt solutions and one percent chloramine-T.
 - 1 g/day tetracycline for 14 days systemically.
 - Home care including daily application of sodium bicarbonate or three percent hydrogen peroxide paste and inorganic salt irrigations.

Generalized Aggressive Periodontitis (GAP)

It is assumed that few of the individuals previously classified as having rapidly aggressive periodontitis would be considered to be having GAP.

Etiology

- *Actinobacillus actinomycetemcomitans* along with a diverse microbiota.
- Defective neutrophil or monocyte function.

Clinical Features

- Usually affects individuals under 30 years of age
- Generalized involvement of the permanent teeth; more than 30 percent of sites are involved.
- Generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors.
- May also include patients previously characterized as having rapidly progressive periodontitis.
- Subgingival tissues show the presence of gram-negative rods including *P. gingivalis* and exhibit suppressed neutrophil chemotaxis.
- Qualitatively *P. gingivalis*, *A. actinomycetemcomitans* and *Tannerella forsythia* are frequently detected in the scant plaque that is present.
- Compared to LAP a weaker antibody response to *A. a.* is seen which supports the hypothesis that antibodies function to limit the disease process.
- The destruction often appears episodically, with periods of advanced destruction followed by stages of quiescence of variable length (weeks to months or years).
- Patients often have small amounts of bacterial plaque associated with the affected teeth. However, the amount of plaque seems inconsistent with the amount of periodontal destruction.
- The gingival tissue could be severe, acutely inflamed, proliferating, ulcerated and fiery red with spontaneous bleeding and suppuration. This usually occurs in the destructive stage in which attachment and bone are actively lost.
- Another gingival response shows absence of inflammation and presence of some degree of stippling, although with deep pockets. This response coincides with periods of quiescence in which the bone level remains stationary.
- Some patients may also have systemic manifestations such as weight loss, mental depression and general malaise.

Radiographic Features

- The radiographic picture may range from severe bone loss associated with the minimal number of teeth to advanced bone loss affecting the majority of the teeth.
- Rapidity of the bone loss indicated by radiographs taken at different times illustrates the aggressive nature of this disease.

Risk Factors

- **Microbiologic factors:** Increase in levels of *A. actinomycetemcomitans*.
- **Immunologic factors:** Human leukocyte antigens mainly HLA A9 (candidate markers) and B15 antigens are

consistently associated with aggressive periodontitis. Functional defects of polymorphonuclear leukocytes, monocytes or both may be seen.

- **Genetic factors:** Segregational and linkage analyses of families with a genetic predisposition suggest that a major gene transmitted through an autosomal dominant mode of inheritance plays a role in generalized aggressive periodontitis.
- **Environmental factors:** Schenkin et al 1995, have suggested that although smoking is implicated it may not have the same impact on attachment levels in younger patients.³⁷

Histopathologic Features

Features are same as for localized aggressive periodontitis but the area of destruction is extensive in this form of gingivitis and more amount of chronic inflammatory cell infiltrate is seen.

Management

1. Conventional periodontal therapy: Patient education, oral hygiene improvement, scaling and root planing, flap surgery and regular recall and maintenance. However, response has been limited and unpredictable.
2. Local irrigation using Keyes technique may be done. Irrigation with inorganic salt solutions and one percent chloramine T. Home care may include daily application of a paste of sodium bicarbonate and three percent hydrogen peroxide.
3. Early diagnosis results in a better outcome than those who are diagnosed at an advanced stage of destruction.
4. Surgical resective therapy: Mainly used to reduce or eliminate pocket depth. However, a less than ideal outcome must be taken into consideration before deciding to treat increased pocket depth surgically.
5. Regenerative therapy: Regenerative materials like bone grafts, barrier membranes and wound healing agents have often been used for intrabony defects, particularly vertical defects with multiple osseous walls.
6. Antimicrobial therapy: Walker and Karpinia, 2002, suggested adjunctive antibiotic treatment frequently results in a more favorable clinical response than mechanical therapy alone.³⁸
7. Microbial testing: Some investigators advocate microbial testing as a necessary means of identifying the specific periodontal pathogens responsible for disease and to select an appropriate antibiotic based on sensitivity and resistance.
8. Local delivery of antibiotics: Primary advantage of local therapy is that smaller total dosages of topical agents can be delivered inside the pocket, avoiding the side effects of systemic antibacterial agents while increasing the exposure of the target microorganisms to higher concentrations. Many different forms of local delivery agents like solutions, gels, fibers and chips are available.

9. Full mouth disinfection: Quirynen et al, 1995, described this concept. It consists of full mouth debridement completed in two appointments within a 24 hour period. In addition to this, the tongue is brushed with a chlorhexidine gel (1 percent) for 1 minute, the mouth is rinsed with a chlorhexidine solution (0.2%) for 2 minutes and periodontal pockets are irrigated with a chlorhexidine solution (1%).³⁹
10. Host modulation: The use of sub-antimicrobial dose of doxycycline (SDD) may help to prevent the destruction of the periodontal attachment by controlling the activation of matrix metalloproteinases, primarily collagenase and gelatinase, from both infiltrating cells and resident cells of the periodontium, primarily the neutrophils.

PREPUBERTAL PERIODONTITIS

Earlier thought to be a rare form of periodontitis found to affect the primary dentition. Now classified as periodontitis as a manifestation of systemic disease because most children with severe periodontal destruction also demonstrate profound immunologic abnormalities. The underlying immune deficiency may vary and includes neutrophil defects and leukocyte adhesion defects. Some cases of severe periodontal destruction are associated with the mutation in the cathepsin C gene in affected children. The subgingival bacterial flora is not much different than that in other forms of periodontal disease. The occurrence of severe destruction at an early age is a reflection of increased host susceptibility, resulting from systemic disease.

CLINICAL FEATURES

- Usually seen in children less than 11 years of age.
- Presence of calculus is scant.
- Disease progression is rapid and destructive primarily affecting the primary molars and incisors.
- It tends to show familial occurrence.
- Usually associated with systemic disease. Infact, identification of severe periodontal destruction in a child may be one of the first signs of systemic disease.

Histopathologic Features

Features are same as for localized aggressive periodontitis but the area of destruction is extensive in this form of gingivitis and more amount of chronic inflammatory cell infiltrate is seen.

Management

1. The primary modality of treatment is similar to that of generalized aggressive periodontitis.
2. Response to treatment is generally found to be poor.

LOCALIZED EARLY ONSET PERIODONTITIS (LOCALIZED JUVENILE PERIODONTITIS) (FIG. 5.15)

As has been described previously, the newer terminology recommends the use of the term aggressive periodontitis for periodontal destruction that becomes clinically significant during adolescence or early adulthood. This disease has been classified into the localized and generalized types. Other terms found in literature used to describe the same pathologic conditions include juvenile, localized juvenile, generalized juvenile, rapidly progressive, severe and prepubertal periodontitis. It is more common in girls and it is usually characterized by a lack of the common clinical signs of periodontal disease (inflammation, bleeding, heavy plaque). There may be a genetic predisposition to juvenile periodontitis and it has been linked with some problems of the immune system. It is mostly caused by *Actinobacillus actinomycetemcomitans*. Some genetic and inherited disorders associated with aggressive periodontitis have been elaborated in Table 5.5.

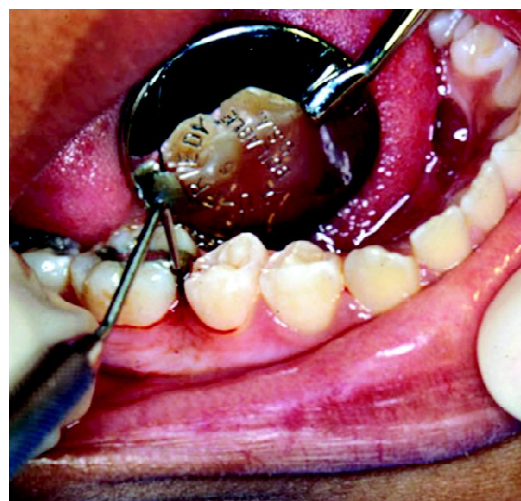


FIGURE 5.15: Localized early onset periodontitis involving the first molar

RADIOGRAPHIC FEATURES

There occur vertical defects of bone. Arc shaped bone loss is seen around the central incisors and permanent first molars.

Management

1. Successful treatment of early onset periodontitis depends on early diagnosis. Children, as well as adults, should receive routine and thorough periodontal evaluations.
2. Treatment of early onset periodontitis begins with the elimination of the bacteria that cause the disease and the control of risk factors.
3. As in adults, treatment consists of scaling and root planing and thorough oral hygiene instructions that include brushing and flossing.
4. Periodontal surgery and systemic antibiotics may be needed.
5. After active treatment, patients should be on a strict supportive periodontal maintenance schedule. This will help prevent the recurrence and progression of periodontal disease.

PAPILLON-LEFÈVRE SYNDROME

It is an inherited disease and tends to form an autosomal recessive pattern. Parents are not affected but both must carry the autosomal genes for the syndrome to appear in the offspring.

Clinical Features

- Males and females are equally affected.
- Disease is usually manifested in childhood.
- Characteristic features include hyperkeratotic skin lesion, severe destruction of periodontium and in some cases, calcification of the dura.

TABLE 5.5: Genetic and inherited disorders associated with aggressive periodontitis

Sr. No.	Disorder	Protein or Tissue defect
1.	Leukocyte adhesion deficiency Type I	CD18 (α -2 integrin chain of leukocyte function-associated molecule)
2.	Leukocyte adhesion deficiency Type II	CD15 (neutrophil ligand for E and P selectins); inborn error in fucose metabolism
3.	Acatlasia	Catalase enzyme
4.	Chronic and cyclic neutropenias	Unknown
5.	Chédiak-Higashi syndrome	Abnormal transport of vesicles to and from neutrophil lysosomes caused by mutations in lysosomal trafficking regulator gene
6.	Ehler-Danlos syndrome (EDS types IV and VIII)	Type III collagen for EDS type IV, unknown for type VIII
7.	Papillon-Lefèvre syndrome	Cathepsin C (dipeptidyl aminopeptidase I)
8.	Hypophosphatasia	Tissue-nonspecific alkaline phosphatase
9.	Trisomy 21	Multiple; critical trisomic region at least 5 Mb long
10.	Prepubertal periodontitis (nonsyndromic)	Cathepsin C
11.	Kindler syndrome	Defect in actin-extracellular matrix linkage caused by loss of function mutations in KIND-1

- Early inflammatory changes followed by rapid bone loss results in exfoliation of teeth (Fig. 5.16).
- The skin lesions consist of hyperkeratosis and ichthyosis of localized areas on palms, soles, knees and elbows (Figs 5.17 A and B).
- All the primary teeth may be lost by 5 to 6 years of age.
- Permanent dentition erupts normally, but they too are lost within a few years due to destructive periodontal disease.

Histopathologic Features

- Marked chronic inflammation of the lateral wall of the pocket with a predominantly plasma cell infiltrate, considerable osteoclastic activity and apparent lack of osteoblastic activity and an extremely thin cementum.
- Composition of bacterial flora is similar to that of chronic periodontitis.
- Spirochete-rich zones in the apical portion of the pockets as well as spirochete adherence to the cementum and microcolony formation of mycoplasma species have been reported.
- Gram-negative cocci and rods appear at the apical border of the plaque.
- No significant alterations have been found in peripheral blood lymphocytes and polymorphonuclear leukocytes.

Hypophosphatasia

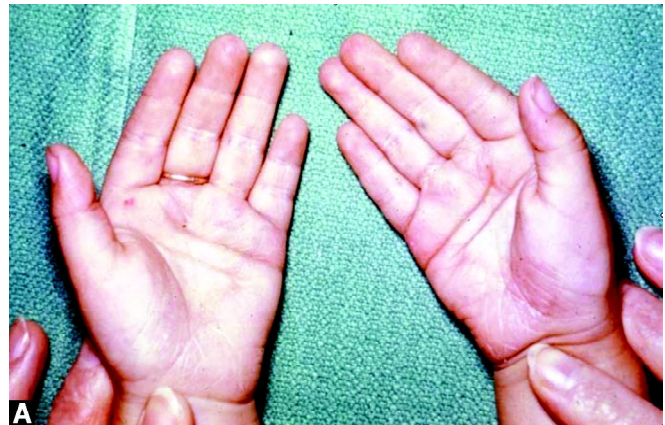
- Rare genetic disease manifested by bone pain with spontaneous fractures.
- Low alkaline phosphatase.
- Excretion of phosphoethanolamine.
- Elevation of serum phosphorus.

Types

Infantile, childhood and adult .



FIGURE 5.16: Pathologic migration of teeth due to bone loss in Papillon-Lefèvre syndrome



FIGURES 5.17A and B: Palmar and plantar keratosis in Papillon-Lefèvre syndrome

Clinical Features

- Premature loss of primary teeth (Fig. 5.18).
- No gingival inflammation.
- Loss of alveolar bone.
- Absence of cementum.

CYCLIC NEUTROPENIA

- Neutropenia is a rare disorder that causes children to have lower than normal levels of neutrophils, a type of white blood cell that destroys bacteria in the blood.
- Periodic episodes of fever and oral ulcerations. When it occurs in periodic cycles, it is termed as cyclic neutropenia. The cycle generally occurs over a period of 21 days.
- Periods of profound neutropenia.
- Onset by 10 years of age.
- 19 to 21 day cycle.
- Course: Usually benign.

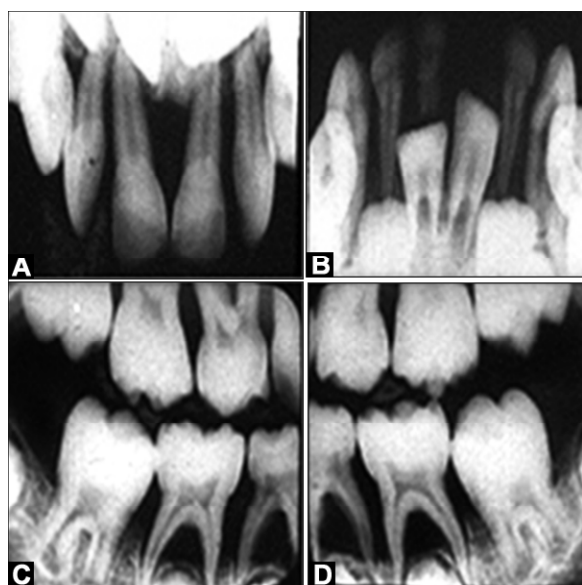
Clinical and radiographic pictures of cyclic neutropenia have been presented in Figures 5.19 and 5.20.



FIGURE 5.18: Premature loss of primary teeth



FIGURE 5.19: Severe gingivitis and ulceration without evidence of inflammation



FIGURES 5.20A to D: Marked destruction of bone in cyclic neutropenia

A more detailed description about this disorder is mentioned in the chapter on *Blood pathologies in children*.

GINGIVAL RECESSION

SELF MUTILATION

Self mutilation may be described as repetitive acts that result in physical damage to the person. It is extremely rare in normal children. However, its incidence in the mentally retarded population is between 10 percent and 20 percent.⁴⁰

Self-mutilation is a learned behavior as it is reliably reinforced by gaining attention each time the behavior is practiced. Any child who willfully inflicts pain or damage on himself or herself should be considered psychologically abnormal. Self-mutilation may serve as an escape from reality. Fisher, 1958, reported that unhappiness and conflict in the home can be hidden more easily from a 15-year-old child than from a 15 week old child.⁴¹

Self-mutilation has also been associated with biochemical disorders such as Lesch-Nyhan and de Lange's syndromes.

Clinical Features

- A frequent manifestation of self-mutilation is biting of the lips, tongue and oral mucosa.
- Self mutilation probably occurs more frequently than is realized because relatively few children will admit the act unless they are observed practicing it. Hence diagnosis is critical.
- Children have been observed to traumatize the free and attached gingival tissues with the finger nail, occasionally to the extent that the supporting alveolar bone has been destroyed.
- Stripping of the gingival tissues unilaterally or bilaterally has been observed, usually with the finger nail or with articles like a pencil or a bobby pin.
- Chronic cheek biting may be practiced occasionally producing large necrotic areas.
- An unconventional sucking habit observed by Stewart and Kernohan, 1973, involves the production of traumatic gingival recession in infants by a segment of the plastic shield of a pacifier being embraced by the lower lip such that the inner surface of the shield bears against the labial aspect of the incisors and the gingival tissues.⁴² This results in an abrasive action during sucking, resulting in gingival injury, recession and loss of alveolar bone.

Management

1. Behavior modification is the primary mode of approach in a child displaying self mutilative behavior. The family can be directed to competent counseling services to treat the emotional problems.

2. An attempt should be made to determine the cause.
3. If it is found to be the result of local dental factors, it should be corrected.
4. Use of restraints, protective padding and sedatives may be used.
5. If the use of restraints and protective padding is unsuccessful, extraction of the selected teeth may be necessary.

ABNORMAL FRENUM ATTACHMENT

Henry, Levin and Tsaknis, 1976, describe a frenum as a mucous membrane fold containing epithelium and connective tissue fibers, but no muscle.⁴³ A normal frenum attaches apically to the free gingival margin so as not to exert a pull on the zone of the attached gingiva, usually terminating at the mucogingival junction.

Most commonly freni are found on the facial gingival surface of the anterior midline of the maxilla, on the facial and lingual gingival surfaces of the anterior midline of the mandible and on the mandibular and maxillary premolar facial area. Some frena have bifid and trifid attachment to the alveolar process.

CLINICAL FEATURES

- An abnormal or high frenum is present when there is inadequate attached gingiva in the terminal insertion area.
- The abnormal frenum attachment is most often observed in the central incisor area though it may involve the labial tissue in the canine areas.
- A close attachment of the frenum to the gingival margin may interfere with proper toothbrush placement, may cause opening of the gingival crevice during function, or may interfere with the speech.
- Abnormal frenum attachments may also be associated with isolated gingival recessions and diastemas, though a cause and effect relationship may or may not be involved.
- Isolated gingival recession may also lead to pocket formation.
- Lip movements may cause the abnormal frenum to pull on the fibers inserting into the free gingival margin. This could lead to food accumulation, inflammation, pocket development between the labial surface of the tooth and the vestibular mucosa.
- Eventually, continued stripping of the labial tissue may occur resulting in subsequent loss of alveolar bone and possibly even the tooth.
- Impedance of speech may occur, especially the /t/, /d/ and /l/ sounds due to a short mandibular lingual frenum inhibiting the tongue from touching the maxillary central incisors.

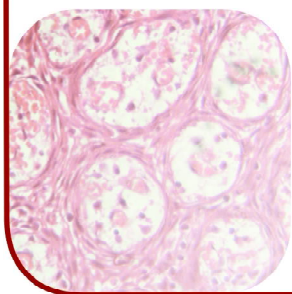
Management

1. Surgical treatment is indicated only if there is stripping of gingival tissue, inability to keep the area clean, inflammation, pocket, persistent midline diastema or impedance in speech.
2. Surgical treatment involves a frenotomy or a frenectomy.
3. Frenotomy involves incision of the periosteal fiber attachment and suturing of the frenum to the periosteum at the base of the vestibule.
4. Frenectomy involves complete excision of the frenum and its periosteal attachment. It is indicated when large, fleshy frenums are involved.

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Cysts in the Pediatric Population

Mayur Chaudhary, Shweta Dixit Chaudhary

CHAPTER OVERVIEW

Introduction
Definition
Classification
Odontogenic keratocyst
Dentigerous cyst
Eruption cyst
Gingival cyst of infant
Midpalatal raphe cyst
Radicular cyst
Residual cyst
Solitary bone cyst
Aneurysmal bone cyst
Calcifying odontogenic cyst

Dermoid cyst
Epidermoid cyst
Teratoid cyst
Thyroglossal tract cyst
Intraoral lymphoepithelial cysts
Lingual cyst of foregut origin
Cystic hygroma
Parasitic cysts:
Hydatid cyst
Cysticercus cellulosae
Cysts of salivary glands:
Mucocoeles
Ranula

INTRODUCTION

Human teeth, which are so casually used each time we eat, talk, swallow, etc. are formed by the complex process of odontogenesis, where normal tooth structure is formed from the odontogenic apparatus. Deviation from the normal process of odontogenesis leads to formation of cysts and tumors. Cysts of odontogenic origin in children are one of the aberrations from the normal process of odontogenesis which form a diverse group of lesions.

DEFINITION

Kramer, 1974 described cyst as a pathological cavity having fluid, semifluid or gaseous contents and which is not created by the accumulation of pus; it is frequently but not always lined by epithelium.¹

CLASSIFICATION²

See Figure 6.1.

ODONTOGENIC KERATOCYST

Philipsen, 1956,³ first described the term odontogenic keratocyst (OKC). It is named odontogenic keratocyst because the epithelial lining of cyst produces keratin that gets filled within the cystic lumen. They are aggressive in nature and thus Toller, 1967,⁴ suggested that they may be regarded as benign cystic neoplasms.

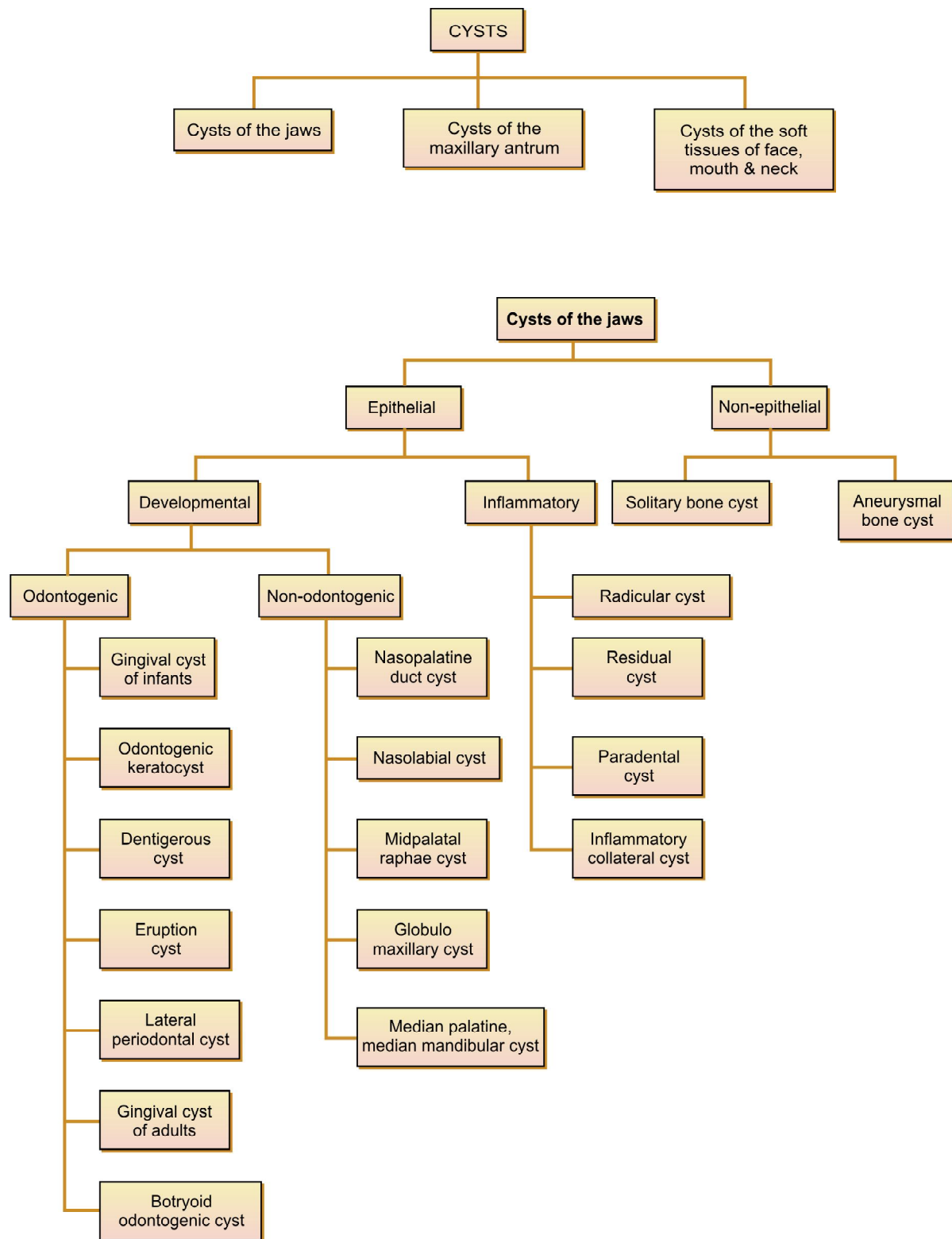
PATHOGENESIS

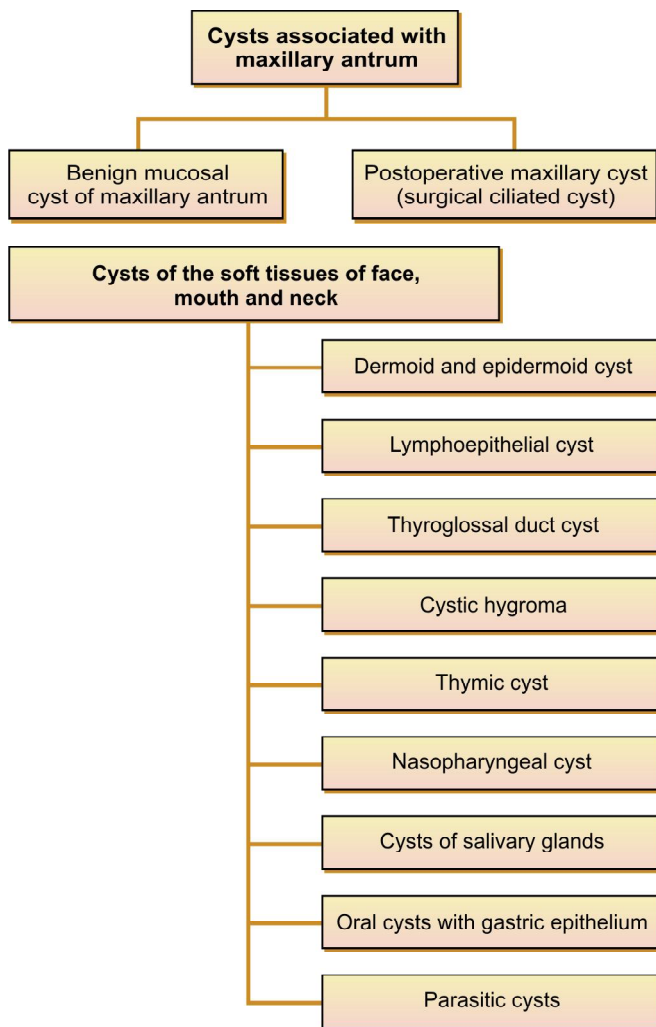
Varying theories regarding its pathogenesis exist:

- Arises from odontogenic epithelium—Dental lamina rests
- Arises from basal cells from the overlying oral epithelium
- Derived from enamel organ in its early stages of development by degeneration of stellate reticulum before calcification of any hard tissue of teeth
- Satellite/daughter cyst—Arises from dental lamina rests.

TYPES OF ODONTOGENIC KERATOCYST (FIG. 6.2)

Main, 1970, described an 'envelopmental' variety of cyst radiographically where an OKC embraces an adjacent unerupted



FIGURE 6.1: Classification of cysts²

tooth.⁵ The cysts that were formed in place of tooth were termed as 'replacement' variety. Those that occurred in ascending ramus were named as 'extraneous' and those that occurred adjacent to the tooth roots were termed as 'collateral' variety.

Replacemental variety is also called as **primordial cyst**.

One more variety of OKC is **follicular keratocyst** (Fig. 6.3).

A tooth surrounded by its follicle erupts into a keratocyst cavity in the same way as it erupts in the oral cavity.

CLINICAL FEATURES

- Seen in 1st to 9th decade of life (more often in the 2nd, 3rd and 5th decades)
- *Meera et al*, 1996, made a pediatric institutional review of OKC's. Their ages ranged from 8 to 18 years. They found OKC's in 11 children⁶
- Incidence is 12 to 13 percent of total jaw cysts

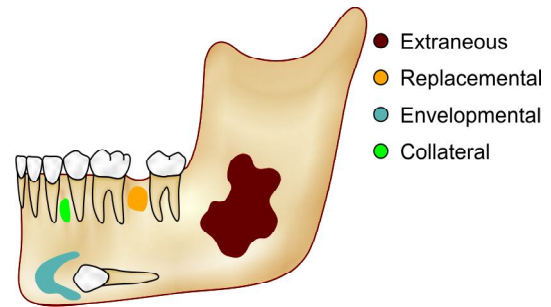
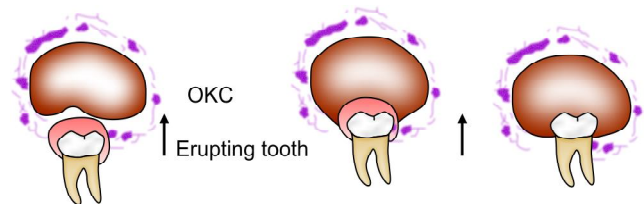
FIGURE 6.2: Types of OKC (Main-1970)⁵

FIGURE 6.3: Follicular keratocyst



FIGURE 6.4: Odontogenic keratocyst presenting as a painful swelling in the lower left posterior region of the jaw

- Seen more often in males as compared to females
- Occurrence in mandible is more than in maxilla
 - In mandible more common in posterior region (Fig. 6.4)
 - In the mandibular posterior region, more often seen in ramus/angle of mandible.
- Signs and symptoms associated with the cyst often present as pain, swelling, discharge and paresthesia of lower lip
- OKC extends in the medullary cavity—Hence observable expansion of bone occurs late



FIGURE 6.5: Odontogenic keratocyst with multilocular radiolucent area and well-defined anterior margin extending towards premolar region on left side and towards the canine region on the right side

In Maxilla—Buccal cortical plate expansion is more

In Mandible—Both buccal and lingual cortical plate expansion is seen

- Syndrome associated with odontogenic keratocyst: Naevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Its salient features are:
 - Multiple OKCs
 - Multiple basal cell carcinomas
 - Abnormalities of Ca^{++} and PO_4^- metabolism which are manifested by calcification of falx cerebri, bifid rib and vertebral deformities.

RADIOGRAPHIC FEATURES (Fig. 6.5)

- Small, round or ovoid radiolucent areas demarcated with sclerotic margins
- Unilocular more often than multilocular
- Scalloped margins are present which are mistaken for multilocularity
- Downward displacement of inferior alveolar canal
- Resorption of lower cortical plate of mandible as well as perforation of bone
- Fracture of the mandible may occur
- Displacement of roots but resorption of roots is rarely seen.

HISTOPATHOLOGIC FEATURES

Epithelium

- Parakeratinized (80%) or Orthokeratinized (20%) stratified squamous epithelium
- Corrugated epithelium (Fig. 6.6)
- 5 to 8 cell layer thick
- No rete ridges (rete pegs)
- Basal cells are columnar to cuboidal and show palisading.

Connective Tissue Wall

- Fibrous capsule of the cyst is usually thin
- Epithelium—connective tissue attachment is weak and tends to separate from each other in many areas
- Few to many daughter/satellite cysts are seen.

Rarities: Cholesterol clefts, melanin pigment, hyaline bodies, mast cells, mucous metaplasia.

Recurrence rate is very high in OKC (20–60%)

Why does OKC Recur?

- Tendency to multiplicity is due to satellite cyst formation
- Incomplete removal of lining may occur because lining is thin and fragile and attachment between the two is weak
- There is a particular predisposition to form OKC from dental lamina rests
- Proliferation of basal cells of oral epithelium.

Expansion of cyst is due to the following factors:

- Hydrostatic pressure
- Active epithelial growth
- Production of bone resorbing factor by the cystic capsule/wall
- Accumulation of certain proteins, e.g. keratin.

Management

1. **Ghali and Connor, 2003**, suggested surgical enucleation of the lesion.⁷
2. **Schmidt, 2003**, suggested the use of liquid nitrogen cryotherapy for management of OKC's.⁸
3. **Stoleinga, 2003**, suggested excision of the overlying, attached mucosa in conjunction with cyst enucleation and treatment of bony defect with Carnoy solution.⁹
4. **Pogrel, 2003**, suggested decompression and marsupialization.¹⁰



FIGURE 6.6: Histopathologic picture of odontogenic keratocyst showing a corrugated epithelium, 6 to 8 cells thick

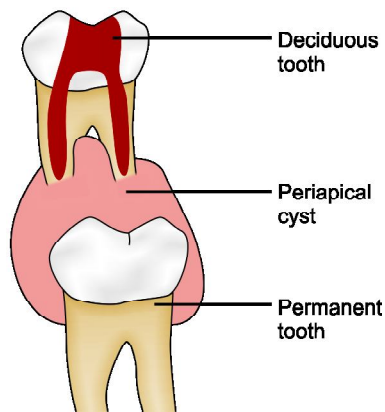


FIGURE 6.7: Radicular cyst mimicking dentigerous cyst

DENTIGEROUS CYST (FOLLICULAR CYST)

Browne has explained the meaning of dentigerous as 'tooth bearing'.¹¹

PATHOGENESIS

- Occurs due to accumulation of fluid
 - Either between the reduced enamel epithelium and the enamel **or**
 - Within the enamel organ itself.

Lustmann and Shear, 1985,¹² Wood et al, 1988,¹³ suggested that sometimes radicular cyst (periapical cyst) may mimic a dentigerous cyst (Fig. 6.7).

CLINICAL FEATURES

- Incidence is 16 to 18 percent of total jaw cysts (2nd highest in occurrence)
- Seen in 1st to 3rd decade of life
- Seen more often in males than females
- Occurrence in mandible is more than in maxilla with the ratio of 2:1. Incidence in tooth no.: (38, 48) > (13, 23) > (34, 35, 44 and 45) > (18, 28) (FDI system)
- Seen more often in whites as compared to blacks
- Bodner, 2002, in a series of 69 pediatric patients with cystic lesions of jaws found 31 were dentigerous cysts¹⁴
- In the presence of a dentigerous cyst, the tooth of the permanent series is missing (impacted)
- At times, a supernumerary tooth or cystic odontome may be involved in cyst formation, then the complement of teeth in the arch remains the same
- Patient does not present with pain unless infected
- Swelling is rarely seen (uncommon).

RADIOGRAPHIC FEATURES

- Small round, ovoid unilocular radiolucent areas associated with crowns of unerupted teeth

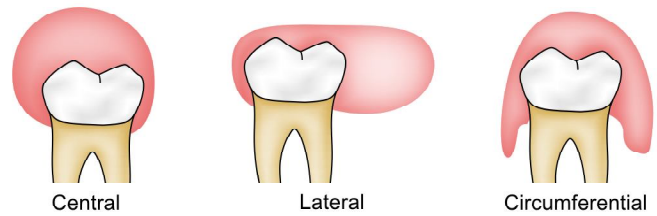


FIGURE 6.8: Types of dentigerous cysts

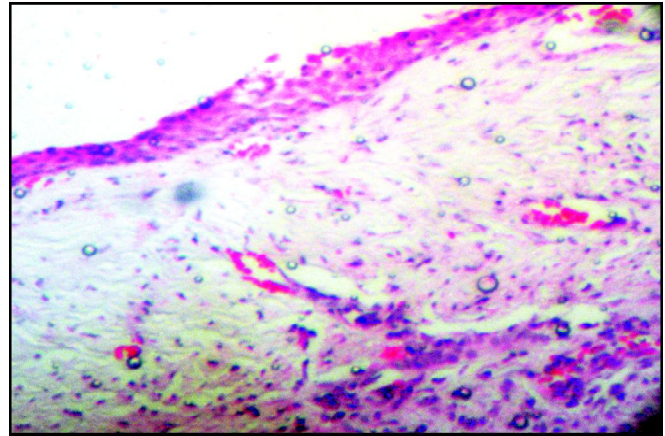


FIGURE 6.9: High power view of dentigerous cyst showing a thin, regular lining of non-keratinized squamous epithelium

- Well-defined sclerotic margins unless infected
- Rarely resorption of lower cortical plate of mandible
- Displacement of roots may be seen but rarely is resorption of roots seen
- Radiographically, three different varieties of dentigerous cysts have been described (Fig. 6.8):
 - In central variety, the crown is enveloped symmetrically.
 - Dilatation of the follicle on one aspect of crown results in lateral variety of dentigerous cyst.
 - In circumferential variety, the entire tooth is enveloped by the cyst.

HISTOPATHOLOGIC FEATURES

Cyst is always attached to the neck (CEJ) of the tooth.

Epithelium

- Is in fact reduced enamel epithelium (Fig. 6.9)
- Lining of the cyst is thin—2 to 3 layers of flat or cuboidal cells
- Non-keratinized
- Occasionally, the lining might form keratin by metaplasia.

Connective Tissue Wall

- Thin fibrous cyst wall (which is derived from dental follicle) is present

- Consists of young fibroblasts widely separated by stroma and ground substance
- **Shibata et al, 2004**, in their study on 70 patients under the age of 16 years found that inflammatory change at the apex of a deciduous tooth may be responsible for initiating a dentigerous cyst of the permanent successor.¹⁵

Rarities: Mucous metaplasia of the lining, cholesterol clefts are seen.

Complications

- Ameloblastoma
- Mucoepidermoid carcinoma
- Squamous cell carcinoma.

Management

1. Conservative surgical removal (enucleation) of the cyst followed by orthodontic treatment.
2. **Hyomoto et al, 2003**, investigated dentigerous cysts involving 47 mandibular premolars and 11 maxillary canines in pre-adolescent children and suggested that a period of 100 days after marsupialization is the critical time for deciding whether to extract or to use traction.¹⁶

ERUPTION CYST

It is a type of dentigerous cyst occurring in the soft tissues.

PATHOGENESIS

Similar to dentigerous cyst.

CLINICAL FEATURES

- **Bodner, 2002**, in a series of 69 pediatric patients with cystic lesions of jaws reported 15 eruption cysts indicating a higher frequency of cystic lesions of jaws in children with these cysts¹⁴
- **Aguilo et al, 1998**, in a series of 27 patients reported 36 eruption cysts¹⁷
- **Bodner et al, 2004**, reported the cysts associated with natal teeth in 2 cases. The primary mandibular central incisors and permanent first molars were the teeth most frequently involved, and boys were affected twice as often as girls¹⁸
- **Ramon Boj and Garcia-Godoy, 2000**, reported a case of a 15 month old child with 6 eruption cysts¹⁹
- **Kuczek et al, 2003**, reported that eruption cysts developed in a boy treated with cyclosporin A following a heart transplant²⁰
- They are seen more frequently clinically and some burst spontaneously
- These are usually not excised and are therefore not submitted for histological examination



FIGURE 6.10: Eruption cyst presenting as a painless swelling in the maxillary anterior region

- Cyst produces a smooth swelling over the erupting tooth, which may be of normal color or slightly bluish in color (Fig. 6.10)
- Swelling is soft, fluctuant and painless
- Deciduous anterior and molar region, permanent anterior and premolar region are the common sites where eruption cyst is often observed.

RADIOGRAPHIC FEATURES

Cyst may throw a soft tissue shadow, but there is usually no bone involvement; except that the dilated and open crypt may be seen on the radiograph.

HISTOPATHOLOGIC FEATURES (Fig. 6.11)

- Hematoxylin and eosin stained section of the lesional tissue shows a covering of keratinized stratified squamous epithelium
- Underlying connective tissue is fibrous
- 2 to 4 cells thick stratified squamous epithelium resembling reduced enamel epithelium is sometimes seen with cystic space.

Management

1. No treatment is required in most cases. The cyst bursts on its own and the tooth erupts into the oral cavity.
2. Marsupialization: The dome of the cyst is excised, exposing the crown of the tooth which is allowed to erupt.

GINGIVAL CYST OF INFANT (GCOI) AND MIDPALATAL RAPHAEE CYST (MPRC)

Both these entities are discussed together as they share the same clinical features.

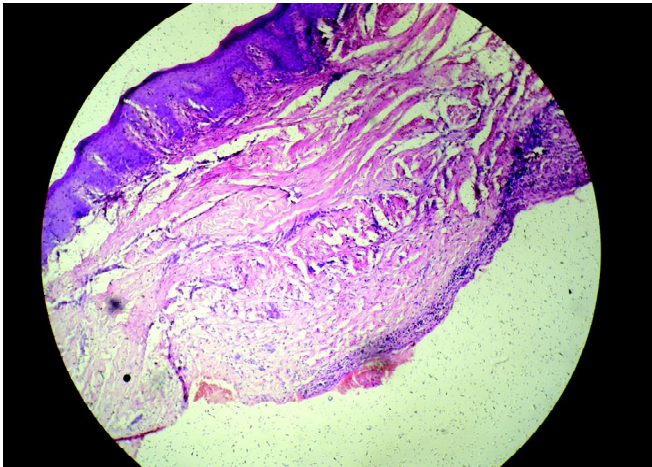


FIGURE 6.11: Histopathologic picture of eruption cyst showing a covering of keratinized stratified squamous epithelium, underlying fibrous connective tissue and 2 to 4 cells thick reduced enamel epithelium

But gingival cyst of infant is odontogenic in origin and midpalatal raphae cyst (MPRC) is non-odontogenic in origin.

PATHOGENESIS

- Gingival cyst of infant arises from dental lamina rests (some open into the oral cavity and some are involved with teeth).
- Midpalatal raphae cyst—Arises from epithelial inclusions at the line of fusion of palatal folds and nasal processes (after birth these inclusions usually atrophy and become resorbed).

CLINICAL FEATURES

- Gingival cyst of infant is mainly seen in newborn infants, but they are rarely seen after three months of age
- Most of them either undergo involution and disappear or rupture through the surface epithelium
- Nodular growths seen on the midpalatal raphae region are termed as **Epstein's pearls** (Fig. 6.12) and on alveolar ridges (buccal and lingual) are known as **Bohn's nodules** (Fig. 6.13)
- **Ikemura et al, 1983**, in their study on 541 Japanese neonates, reported a frequency of 89 percent of these cysts²¹
- **Dilley et al, 1991**, reported a frequency of 50 percent of palatal and alveolar cysts in neonates²²
- **Liu and Huang, 2004**, reported a frequency of 94 percent in 420 Taiwanese neonates.²³

HISTOPATHOLOGIC FEATURES (SAME FOR BOTH)

- Thin lining of stratified squamous epithelium with parakeratotic surface and cystic cavity (lumen) filled with keratin



FIGURE 6.12: Epstein's pearls



FIGURE 6.13: Bohn's nodules

- Basal cells are flat
- As a result of cystic pressure on the oral epithelium, the latter might appear as atrophic.

Management

No indication for treatment. Once their contents are expelled, they atrophy and disappear.

RADICULAR CYST (PERIAPICAL CYST)

Radicular cysts are the most common inflammatory cysts and arise from the epithelial residues in the periodontal ligament as a result of periapical periodontitis following death and necrosis of the pulp.

PATHOGENESIS

- Radicular cyst arises from odontogenic epithelial residues in the periodontal ligament.
- Caries → Inflammation of pulp → Death and necrosis of pulp → Cyst at the apex of root.

THREE PHASES

Phase of Initiation

Meghji et al, 1996, showed that higher levels of bacterial endotoxins initiate the proliferation of epithelial cell rests of Malassez.²⁴

Phase of Cyst Formation

The most widely accepted theory, postulates that a cyst cavity forms within a proliferating epithelial mass in an apical granuloma by degeneration and necrosis of the cells in the center.

Phase of Enlargement

Toller, 1970, hypothesized that osmosis is responsible for growth and enlargement of the radicular cyst.²⁵

CLINICAL FEATURES

- Incidence of 50 to 55 percent of total jaw cysts (highest occurrence)
- Occurs most frequently in 3rd to 4th decade of life (but any age group may be affected)
- More common in males than females
- Occurrence in maxilla is more as compared to mandible. In maxilla, occurrence in anterior region is most common.
- Deciduous teeth involvement is very rare. 0.5% of all radicular cysts as recorded in the University of Witswatersrand over a period of 25 years
- Deciduous teeth when involved are usually the primary molars with caries being the most common etiological factor, as reported by **Lustmann and Shear, 1985** (Fig. 6.14).¹² In 23 cases of the age range 4 to 12 years, they reported 9 cases with buccal expansion and in 8 cases permanent tooth buds were displaced
- **Lustmann and Shear, 1985**, reported only 28 cases of radicular cyst in 1898 patients¹²
- Radicular cyst is usually symptomless, found on routine radiographic examination of non-vital pulp
- At first the enlargement is bony hard but as the cystic cavity increases in size the covering bone becomes very thin and the swelling exhibits **springiness** (Fig. 6.15)
- Only when the cyst completely erodes the bone, will the lesion appear fluctuant



FIGURE 6.14: Radicular cyst, associated with carious primary molars. Deviated eruption of maxillary first premolar can be seen

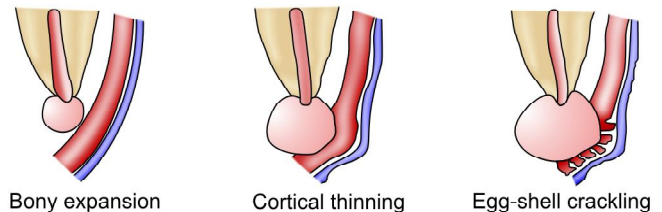


FIGURE 6.15: Enlargement of radicular cyst

- In maxilla, buccal and/or palatal expansion of bone is seen, whereas, in mandible, labial/buccal expansion but rarely lingual expansion is seen
- Sinus formation from the cyst cavity onto the surface of the oral mucosa or skin is occasionally seen.

RADIOGRAPHIC FEATURES (Fig. 6.16)

- Round, ovoid radiolucency surrounded by a narrow radio-opaque (sclerotic) margin which extends from the lamina dura of the involved tooth
- In rapidly enlarging cyst or highly infected cyst the radio-opaque margin may not be present
- Root resorption may occur but is rare, displacement of adjacent tooth roots may be seen.

HISTOPATHOLOGIC FEATURES

Epithelium

- Non-keratinized stratified squamous (1-50 cell layer thick) (Fig. 6.17)
- Proliferation of epithelial lining with arcading pattern (Fig. 6.18)



FIGURE 6.16: Radiographic picture of a radicular cyst, associated with carious primary molars

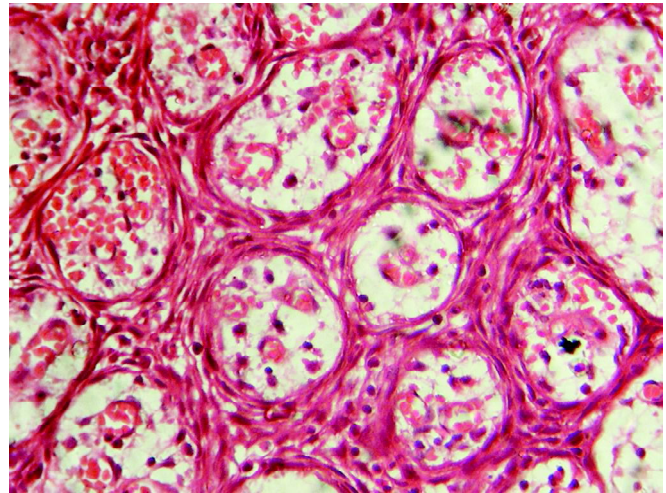


FIGURE 6.18: High power view of radicular cyst showing arcading pattern of the epithelium

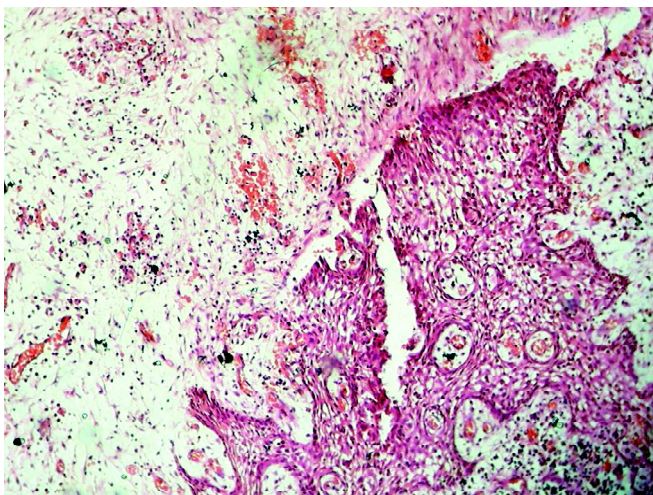


FIGURE 6.17: Low power view of radicular cyst showing arcading pattern of the epithelium. Connective tissue shows blood vessels, collagen fibers and inflammatory cells

- Inflammatory cells are present, mostly neutrophils
- Mucous cells were observed in 40% of the cases (incidence increases with age)
- Hyaline bodies, called as **Rushton's Bodies** (rarely seen in connective tissue wall).

Connective Tissue Wall

Composed of three layers:

1. Inner granulomatous layer
2. Intermediate layer
3. Outer fibrous connective tissue layer.

Rushton Bodies

- Present in epithelium (rarely in connective tissue)
- Measure about 0.1 mm
- Linear, straight, curved or hair-pin shaped and sometimes concentrically laminated
- Brittle and fracture frequently during histological sectioning
- Circular hyaline bodies are also seen with clear outer layer surrounding a central granular body.

What are Rushton bodies?

- They are keratinized secondary enamel cuticle
- They are secretory products of odontogenic epithelium
- Thrombi in the venules of connective tissue.

Types of Rushton bodies

- Type I—Has no central granular component.
- Type II—Fine grained matrix which encloses the coarse-grained foreign material and undergoes a different degree of homogenization.

Cholesterol crystals are found in most of the mature radicular cysts (Fig. 6.19).

Source of Cholesterol

- Released from disintegrating RBCs
- Degeneration and disintegration of lymphocytes, plasma cells and macrophages
- Circulating plasma lipids

Once the cholesterol crystals are deposited—It evokes a foreign body giant cell reaction.

Cholesterol crystals in the connective tissue of radicular cysts get dissolved in the chemical reagents used during tissue processing, leaving empty spaces as seen within the connective

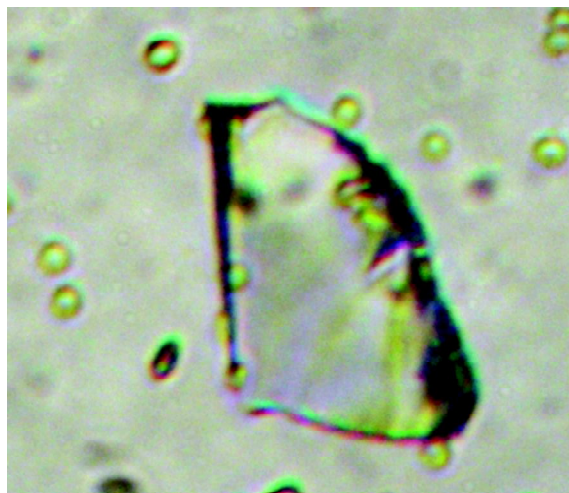


FIGURE 6.19: Radicular cyst focused on a cholesterol crystal

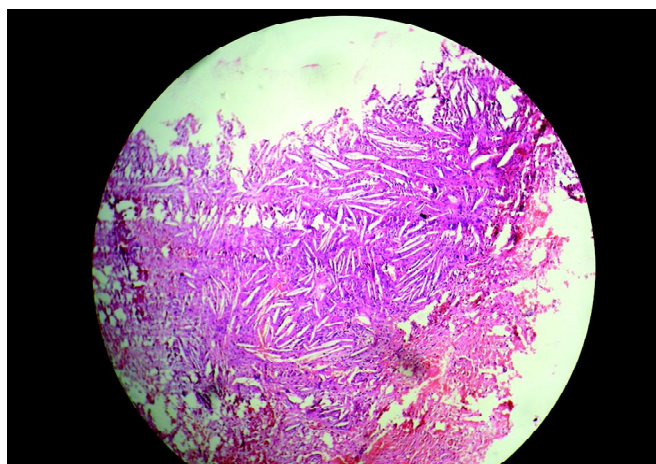


FIGURE 6.20: Histopathologic picture of radicular cyst showing cholesterol clefts

tissue in hematoxylin and eosin stained section. These empty spaces are then termed as cholesterol clefts (Fig. 6.20).

Complications: Very rarely, may undergo a carcinomatous change.

Management

1. Endodontic treatment of the offending tooth often results in regression of the cyst.
2. Surgical removal with/without extraction of the offending tooth

RESIDUAL CYST (Fig. 6.21)

Quite often a radicular cyst remains behind in the jaws after removal of the offending tooth.

High and Hirschmann, 1986, showed that ages of patients varied from 1 month to 20 years.²⁶

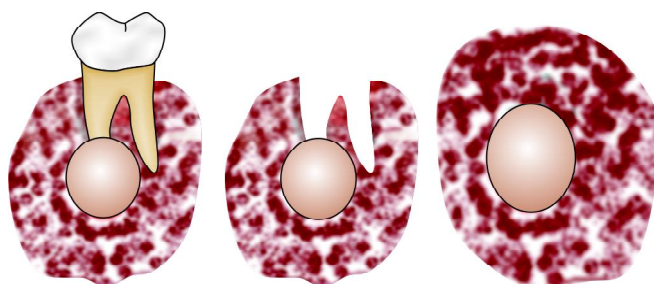


FIGURE 6.21: Formation of a residual cyst

SOLITARY BONE CYST (SBC) (Traumatic, Simple, Hemorrhagic Bone Cyst)

It is a pseudo cyst, as these categories of lesions are usually fluid filled or empty intraosseous lesions found most commonly in the proximal metaphyseal region of the long bones in children and adolescents.

HOWE'S CRITERIA FOR PSEUDOCYST

- Cyst should be single
- Should have no epithelial lining
- Should show no evidence of acute or chronic infection
- Should contain principally fluid and not soft tissue.

PATHOGENESIS

- Not known
- Various hypotheses have been put forth to explain the pathogenesis of a solitary bone cyst:
 - Trauma to bone causes intermedullary hemorrhage. Failure of early organization of hematoma in the marrow spaces and subsequent liquefaction of the clot leads to formation of solitary bone cyst.
 - Mesenchymal cells which usually form bone or cartilage fail to do so. Instead of forming bone or cartilage, mesenchymal cells form synovial tissue. Thus, solitary bone cyst might originate as multiple synovial cavities which later coalesce to form a larger lined defect.

CLINICAL FEATURES

- Diagnosed by chance on routine examination
- Occurs in age range 2 to 35 years but more common in 2nd decade
- In Howe's analysis, 1965, the patients ranged in age from 2.5 to 35 years²⁷
- Sheffield's analysis of 36 cases showed the presence of 53 percent of the lesions in children less than 16 years of age²⁸
- Occurs with equal frequency in males and females
- Occurrence in mandible is more compared to maxilla. Mandibular posterior region is most often involved



FIGURE 6.22: Radiographic picture of a solitary bone cyst showing a radiolucent area with an irregular but definite edge. Lesion remained undiagnosed since childhood

- Swelling, pain, labial paresthesia may occur but are rare
- Previous history of trauma may be present
- All related teeth are vital.

RADIOGRAPHIC FEATURES (FIG. 6.22)

- Cyst appears as a radiolucent area with an irregular but definite edge
- Scalloping is a prominent feature.

HISTOPATHOLOGIC FEATURES

- No epithelial lining
- Consists of loose vascular fibrous tissue membrane of variable thickness
- Fibrin with RBCs are seen
- Hemorrhage and hemosiderin pigments are usually present
- The adjacent bone when included in the specimen shows osteoclastic resorption.

Management

1. Surgery is the treatment of choice.
2. Cyst lumen is opened to reveal an empty cavity, the cyst wall is then curetted. In few cases, blood or sero-sanguinous fluid may be present. Precaution is required to prevent damage to the inferior alveolar nerve.

ANEURYSMAL BONE CYST (ABC)

This is also a pseudo cyst. The term "aneurysmal bone cyst" was suggested by **Jaffe and Lichtenstein, 1942**, to describe the characteristic **blow out** of the bone (Fig. 6.23).²⁹

PATHOGENESIS

- Pathogenesis of aneurysmal bone cyst is controversial
- May be due to trauma to the bone, although there is little evidence to support this

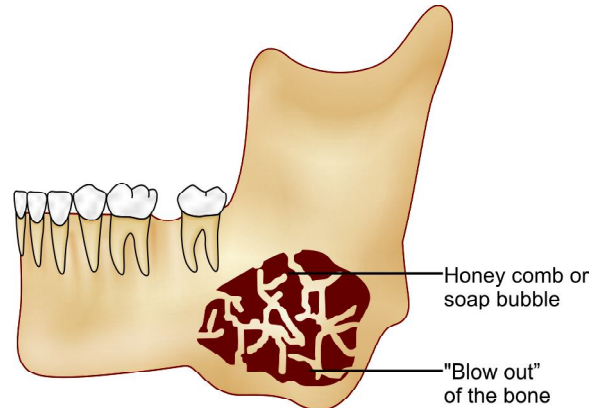


FIGURE 6.23: Aneurysmal bone cyst showing the typical blow out of the bone

- Cyst may result from vascular disturbances in the form of sudden venous occlusion
- Pre-existing lesions (fibrous dysplasia, ossifying fibroma, giant cell tumor, giant cell granuloma, osteoblastoma, solitary bone cyst, chondroblastoma and myxofibroma) may initiate an arterio-venous malformation which may lead to the formation of aneurysmal bone cyst.

CLINICAL FEATURES

- Occurs between 1st-3rd decade of life
- Jones and Franklin, 2006, reported only 11 cases of aneurysmal bone cyst over a period of 30 years, in the Sheffield series. This was a mere 0.15 percent of the 7224 jaw cysts. The lesion was relatively more common in children accounting for 0.7 percent of the 590 jaw cysts in patients lower than 16 years old²⁸
- Seen most commonly in females as compared to males
- Occurrence in mandibular posterior region is more common than in maxilla
- Presents as swelling of the jaws, rarely painful
- Enlargement is rapid and malocclusion frequently becomes progressively worse
- History of displacement of teeth may be present
- If lesion perforates the cortex then **egg-shell crackling** is evident.

HISTOPATHOLOGIC FEATURES

- Lesion consists of many capillaries and blood filled spaces (not lined by endothelial cells) of varying sizes lined by flat spindle cells, separated by delicate loose-textured fibrous tissue (Fig. 6.24)
- Blood filled spaces have no endothelial lining, no-elastic or smooth muscle around them
- Giant cells are seen surrounding the blood spaces

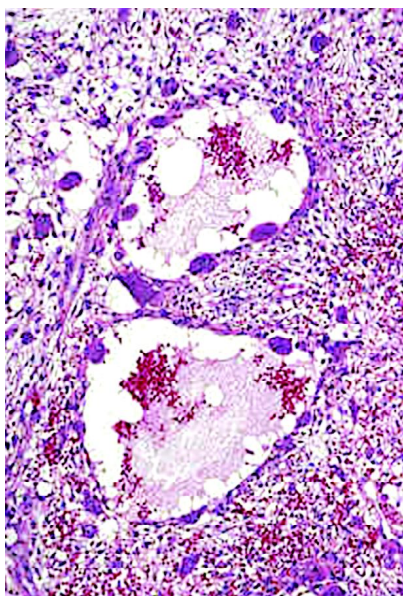


FIGURE 6.24: Histopathologic picture of an aneurysmal bone cyst showing blood filled spaces surrounded by giant cells

- Osteoid bone formation in few areas is also evident
- Fibroblasts, histiocytes and hemosiderin pigment are also seen in areas
- Solid areas of cyst may have the appearance of a primary lesion.

Management

1. According to *El-Deeb et al, 1980*, thorough curettage with removal of primary tumor if any is the preferred treatment.³⁰
2. According to *El-Deeb et al, 1980*, recurrence is up to 26 percent. It depends on the primary tumor (Ossifying fibroma cases have shown high recurrence rate).³⁰

CALCIFYING ODONTOGENIC CYST (Gorlin cyst; Odontogenic ghost cell tumor)

Calcifying odontogenic cyst (COC) was considered to be quite a confusing entity. *Praetorius et al, 1981*, concluded that what had previously been regarded as a calcifying odontogenic cyst actually comprised two entities: a cyst and a neoplasm.³¹ In the latest WHO publication on odontogenic tumors (*Praetorius and Ledesma-Montes, 2005*), it was classified as a benign odontogenic tumor and was renamed calcifying cystic odontogenic tumor (CCOT).³²

PATHOGENESIS

It may arise from:

- Reduced enamel epithelium
- Remnants of odontogenic epithelium.

Dentinoid or odontome may be found in the cyst wall, induced by the lining epithelium.

CLASSIFICATION {PRAETORIUS et al (1981)}³¹

- | | |
|---------|---|
| Type I | A. Simple unicystic type |
| | B. Odontome producing type |
| | C. Ameloblastomatous proliferating type |
| Type II | Neoplasm with some histopathological features of COC. |

CLINICAL FEATURES

- *Praetorius, 2006*, reported the youngest patient with calcifying odontogenic cyst of one year and the oldest patient of 82 years indicating a wide age-range with an impressively high peak in the second decade
- Incidence of 1 to 2 percent of total jaw cysts
- Males are affected more often as compared to females
- Occurs with equal frequency in mandible and maxilla. Anterior part of the jaw is affected more often
- Swelling is the most frequent complaint
- Rarely is the swelling accompanied by pain
- Lingual expansion of cortical bone is noted
- Occasionally the COC may perforate the cortical plate and extend into the soft tissue.

RADIOGRAPHIC FEATURES

- Regular outlined radiolucent lesion with well demarcated margins
- Lesion is usually unilocular/occasionally multilocular.
- Irregular opacities in the radiolucency may be seen (calcified bodies)
- Displacement of teeth is a common finding
- Resorption of adjacent roots is a frequent finding
- Local expansion sometimes occurs and perforation of the cortical plate may be evident.

HISTOPATHOLOGIC FEATURES (FIG. 6.25)

- Epithelium may be regular, 6 to 8 cells thick
- The epithelial lining has characteristic odontogenic features with a prominent basal layer consisting of palisaded columnar or cuboidal cells and hyperchromatic nuclei which are polarized away from the basement membrane
- Sometimes the epithelium represents squamous cells and sometimes stellate reticulum like cells
- Ghost cells are seen in the epithelial lining. These cells sometimes penetrate the connective tissue wall and evoke a foreign body giant cell reaction.
- *Ghost cells:*
 - They are pale and eosinophilic and although the cell outlines are usually well-defined, they may sometimes be blurred so that groups of them may fuse

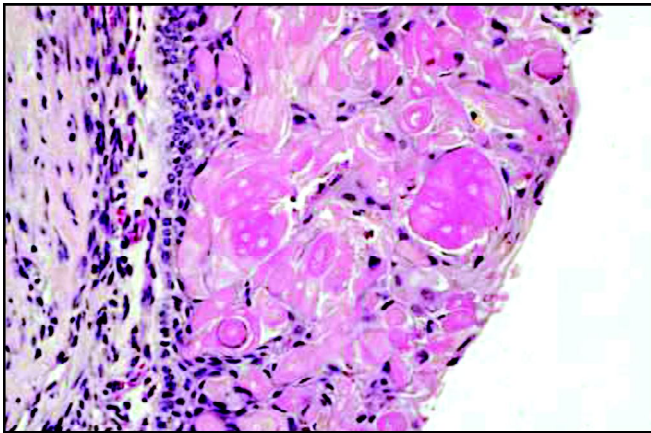


FIGURE 6.25: Histopathologic picture of calcifying odontogenic cyst showing ghost cells in the epithelial lining

- A few ghost cells may contain nuclear remnants but these are in various stages of degeneration and in the majority, all traces of chromatin have disappeared leaving only a faint outline of the original nucleus.
- Ghost cells represent an abnormal keratinization and have an affinity for calcification.
- Some workers believe that it is amelogenin like protein and not keratin.
- Ghost cells are also seen in odontoma, ameloblastic fibro-odontome.

Management

1. Surgical enucleation.
2. If associated with any other odontogenic tumor, wider excision is required.
3. Conservative approach if associated with complex odontome.

DERMOID CYST

It is a developmental lesion occurring in many areas of the body. It is considered to be a hamartomatous tumor containing multiple sebaceous glands and almost all skin adnexa. It may also contain substances such as nails and dental, cartilage-like and bone-like structures.

ETIOLOGY

- Developmental entrapment of multipotential cells
- Sequestration of skin and subsequent implantation of epithelium along the lines of embryonic closure.

CLINICAL FEATURES

- Yoshimura et al, 1970,³³ and Yeschua et al, 1977,³⁴ reported an age incidence between 15-35 years with a wide age-range from birth to senility

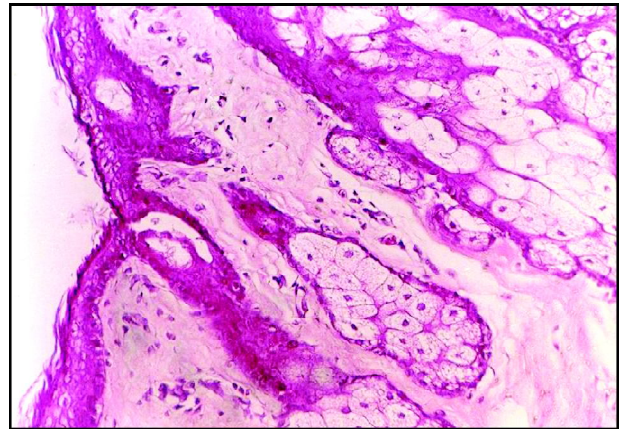


FIGURE 6.26: Histopathologic picture of dermoid cyst showing a lining of stratified squamous epithelium. Numerous sebaceous glands are also evident

- When located above mylohyoid muscle, it displaces the tongue superiorly and posteriorly
- Below mylohyoid, a midline swelling of neck occurs
- The cyst generally appears as painless and slow growing
- It does not have a particular sex predilection
- On palpation, the cyst is soft and doughy because of keratin and sebum in the lumen.

HISTOPATHOLOGIC FEATURES (FIG. 6.26)

- The cyst is lined by stratified squamous epithelium supported by fibrous connective tissue
- Lumen shows keratin or sebum
- Numerous secondary skin structures, including hair follicles, sebaceous glands and sweat glands, may be found.

Management

1. Surgical excision. Those cysts located above the geniohyoid muscle can be removed by the intraoral approach.
2. Below geniohyoid muscle, the extraoral approach should be employed.

EPIDERMOID CYST (Epidermal Inclusion Cyst) (FIG. 6.27)

The term epidermoid cyst is used in a general context, in that, irrespective of the source of the epithelium, the term persists. Was also called as a sebaceous cyst, but this is a misnomer as this cyst is not of sebaceous origin.

ETIOLOGY

- Sequestration or implantation of epidermal rests during embryonal period
- Occlusion of the pilosebaceous unit



FIGURE 6.27: Epidermoid cyst presenting as a soft fluctuant swelling near the outer canthus of eye

- Iatrogenic or surgical implantation of epithelium into the jaw mesenchyme.

CLINICAL FEATURES

- It is indolent in nature and slow to progress
- Remains asymptomatic until secondarily infected
- Presents with pain and tenderness when infected
- Twice more common in men than in women
- Most common in third and fourth decades
- May present with discharge of a cheese-like foul smelling material
- When located orally, may cause difficulty in feeding, swallowing or speaking
- Appears as firm, round, mobile, flesh-colored to yellow or white subcutaneous nodules of variable size
- Central pore or punctum may or may not be present
- May be located on face, scalp, neck, trunk, extremities
- Associated syndromes:
 - Gardner syndrome
 - Basal cell nevus syndrome
 - Pachyonychia congenita.

HISTOPATHOLOGIC FEATURES

- Cystic lining comprises of stratified squamous epithelium with glandular differentiation
- Cyst is filled with desquamated keratin disposed in a laminar pattern (Fig. 6.28)
- Dystrophic calcification and reactive foreign body reaction is associated with the cystic capsule
- Malignant transformation of the cystic capsule may occur.

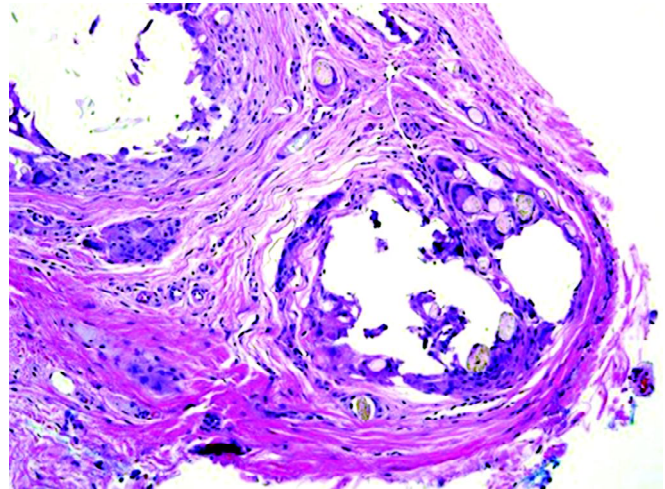


FIGURE 6.28: Histopathologic picture of epidermoid cyst showing a keratin filled cystic cavity

Management

Surgical excision is the treatment of choice.

TERATOID CYST

Occasionally, cysts may be encountered that may have elements derived from ectoderm, endoderm and mesoderm. These are termed teratoid cysts and are the rarest of the developmental cysts of the oral cavity.

CLINICAL FEATURES

- It is a rare entity
- Arises in the floor of the mouth
- *Harada et al, 1995*,³⁵ and *Bonilla et al, 1996*,³⁶ report that the cyst usually presents in neonates, although a case was reported in a 5 year old boy by *Ohishi et al, 1985*.³⁷

HISTOPATHOLOGIC FEATURES

- Cysts are lined by keratinized stratified squamous epithelium, gastrointestinal epithelium or respiratory epithelium.
- Presence of sebaceous glands, sweat glands, cartilage, smooth muscle, striated muscle, neural tissue or bone in the cyst wall.

Management

Surgical excision.

THYROGLOSSAL TRACT CYST (Fig. 6.29)

Luna and Pfaltz, 2001,³⁸ and *Koch, 2005*,³⁹ reported the thyroglossal cyst to be the most common developmental cyst



FIGURE 6.29: Thyroglossal duct cyst presenting as a midline swelling in the neck

of neck accounting for 90 percent of the congenital abnormalities in the neck in children.

PATHOGENESIS

Development of thyroid



Thyroid anlage grows downwards in neck



Residues of epithelial elements that do not atrophy completely give rise to cysts.

CLINICAL FEATURES

- **Allard, 1982**, in a sample of 1316 cases reported 32% cases under the age of 10 years⁴⁰
- Cyst may be found anywhere from posterior portion of tongue to the midline of the neck
- Majority of cases occur below the level of hyoid bone
- When attached below hyoid bone and tongue, the cyst may retract on swallowing
- If infected, a draining sinus tract may occur.

HISTOPATHOLOGIC FEATURES

Findings vary according to location of cysts:

- Lesions above level of hyoid bone demonstrate a lining chiefly of stratified squamous epithelium.
- A ciliated or columnar type of epithelium is usually found in cysts occurring below the hyoid bone.
- Thyroid tissue may be seen within the connective tissue wall.

Management

1. Surgical excision is the treatment of choice.
2. The Sistrunk operation involves removal of a 1cm block of tissue surrounding the duct and a 1 to 2cm portion of the central part of the hyoid bone. The thyroglossal tract should also be traced down to the pyramidal lobe of thyroid gland and to the foramen cecum at the base of the tongue.

INTRAORAL LYMPHOEPITHELIAL CYSTS

Intraoral lymphoepithelial cysts develop within a benign lymphoid aggregate or accessory tonsil of the oral or pharyngeal mucosa. This cyst was first reported by **Parmentier** in 1857 as a hydatid cyst.

PATHOGENESIS

- May arise from epithelial inclusions within oral lymphoid tissues
- May arise as a result of cystic dilatation of tonsillar crypts or superficial ducts of minor salivary glands.

CLINICAL FEATURES

- Mostly occur in the floor of the mouth and tongue
- **Giunta and Cataldo, 1973**, reported a series of 21 patients ranging from 7 to 65 years, including 12 females and 9 males. Of these 17 (80%) involved the floor of the mouth, two were in the soft palate and one each in the retromolar area and the mandibular labial vestibule⁴¹
- **Allard, 1982**, reviewed 105 cases in which he found an age range of 7 to 81 years with a peak frequency of 42 percent in the third decade.⁴⁰
 - 64 percent cases involved males
 - 36 percent cases involved females
 - 69 percent cases involved the floor of the mouth
 - 23 percent cases involved the tongue
 - 8 percent cases involved the soft palate, buccal vestibule and the anterior pillar of fauces.

HISTOPATHOLOGIC FEATURES

- **Buchner and Hansen, 1980**, suggested that the cyst is lined by keratinized (parakeratinized and occasionally orthokeratinized) stratified squamous epithelium devoid of rete ridges⁴²
- Lymphoid tissue is found surrounding the cyst. In a few cases this is present only in a part of the cyst wall
- Lymphoid tissue shows a germinal center, sometimes with only a dense infiltrate of lymphocytes.

Management

Surgical excision is the treatment of choice.

LINGUAL CYST OF FOREGUT ORIGIN

The term lingual cyst is a descriptive term for cysts of foregut origin that arise within the tongue.

CLINICAL FEATURES

- Arise within the tongue.
- **Allard, 1982**, reported that 12 out of 18 cases of this lesion occurred in the first year of life, 3 cases were between the ages 2 to 11 years and two were adult patients where lesion was present since childhood⁴⁰
- **Manor et al, 1999**, found most of the lesions on the dorsal surface of the tongue in the anterior midline area.⁴³

HISTOPATHOLOGIC FEATURES

Cysts are lined by respiratory epithelium, gastric epithelium, intestinal epithelium or combinations of two or three of these types.

Management

Surgical excision.

CYSTIC HYGROMA

Cystic hygroma is a developmental abnormality in which there is a progressive dilatation of the lymphatic channels. It is currently designated as cavernous type of lymphangioma.

CLINICAL FEATURES

- **Bayer and Hardman, 1976**, reported that the lesion is often present at birth; most cases are diagnosed before the age of 2 years.⁴⁴
- In the head and neck region, it produces a swelling, which is often painless and usually compressible.
- The lesion is usually unilateral but the entire side of the neck and lower face may be involved.
- The overlying skin may be blue.
- The swelling tests positive to transillumination.

HISTOPATHOLOGIC FEATURES

Cystic hygroma consists of dilated cystic spaces lined by endothelial cells.

Management

1. Surgical excision. If acute infection occurs prior to resection, surgery should be delayed for at least 3 months.
2. Laser therapy is a recent advancement in the treatment of microcystic lesions.
3. Magnetic resonance—controlled laser-induced interstitial thermotherapy is a novel therapy that has been proposed for treatment of lymphangiomas.
4. The medical treatment of cystic hygroma consists of the administration of sclerosing agents. Sclerosing agents include OK-432 (an inactive strain of group A *Streptococcus pyogenes*), bleomycin, pure ethanol, bleomycin, sodium tetradecyl sulfate and doxycycline.

PARASITIC CYSTS**HYDATID CYST**

Hydatid cysts occur in hydatid disease or echinococcosis.

Etiology

It is caused by the larvae of *E. granulosus*, the dog tapeworm, which resides in the intestinal tract of the dog. The ova may be accidentally ingested by the host. These ova hatch in the upper gastrointestinal tract and are dispersed through the blood vessels to all parts of the body.

Clinical Features

- **Ataoglu et al, 2002**, reported a case of a 6-year-old boy showing a parasitic cyst in the maxillary sinus⁴⁵
- Most of the cases occur in salivary glands, pterygopalatine or temporal fossa areas
- **Bouckaert et al, 2000**, reported two cases of this lesion. One case was reported in submandibular gland of 20-year-old female, the second case occurred in the buccal mucosa of a 6-year-old boy.⁴⁶

Histopathologic Features (Fig. 6.30)

- The cyst consists of three layers:
 1. Outer layer of host origin lined by fibrous tissue showing chronic inflammatory cell infiltrate, eosinophils and giant cells.
 2. Intermediate layer of parasitic origin, whitish, non-nucleated, consisting of delicate laminations.
 3. Inner nucleated germinal layer of parasitic origin.
- Clear, albumin-free cyst fluid containing the so-called 'hydatid sand' consisting of brood capsules and scolices.

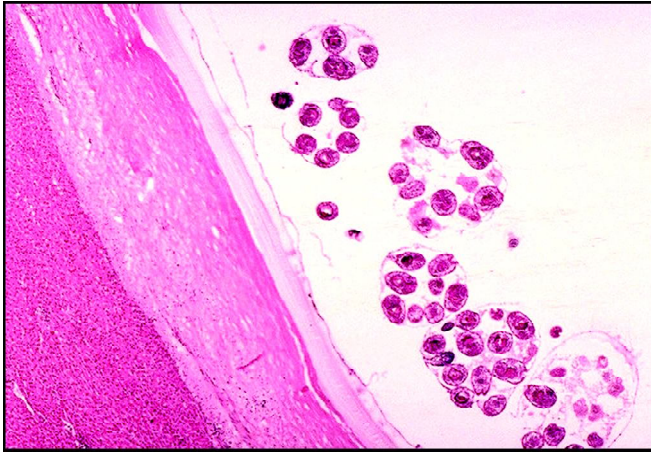


FIGURE 6.30: Histopathologic features of hydatid cyst showing brood capsules and solices lined by fibrous connective tissue containing inflammatory cell infiltrate

- These brood capsules develop originally as minute projections of the germinative layer which develop central vesicles and become minute cysts.
- Scolices of the head of the worm develop in the inner aspects of the brood capsules.

Management

1. Better forms of chemotherapy and newer methods, such as the puncture, aspiration, injection and reaspiration (PAIR) technique are now available but need to be tested.
2. Two benzimidazoles are used, albendazole and mebendazole. Albendazole is administered in several 1-month oral doses (10 to 15 mg/kg/day) separated by 14-day intervals. Mebendazole is administered 40 to 50 mg/kg/day PO for 3 to 6 mo (primary mode of therapy) or for 4 days prior to surgery and then 1 month postoperatively as adjunct.
3. PAIR technique is performed using either ultrasound or CT guidance and involves aspiration of the contents via a special cannula, followed by injection of a scolicidal agent (e.g. formalin, hydrogen peroxide, hypertonic saline, chlorhexidine, absolute alcohol and cetrimide) for at least 15 minutes and then reaspiration of the cystic contents. This is repeated until the return is clear. The cyst is then filled with isotonic sodium chloride solution. Perioperative treatment with a benzimidazole is mandatory (4 days prior to the procedure and 1 to 3 months after).

CYSTICERCUS CELLULOSAE

Cysticercus cellulosae is a parasitic cyst occurring in humans with cysticercosis. Cysticercosis occurs through the larval form

of the pork tapeworm *Taenia solium*. They can act both as the intermediate and the definitive host.

Clinical Features

- **Ostrofsky and Baker, 1975**, reported 3 cases of this lesion of which one occurred as a swelling on the dorsum of the tongue in a 7-year-old child⁴⁷
- **Lustmann and Copelyn, 1981**, reported 2 cases of this lesion of which one case occurred in the tongue of an 11-year-old boy⁴⁸
- The cystic mass contains clear, watery fluid and a coiled white structure apparently attached to the inner aspect of the cyst.

Histopathologic Features

- It shows presence of a dense fibrous outer capsule derived from host tissue
- The capsule consists of a dense inflammatory cell infiltrate consisting predominantly of lymphocytes, plasma cells and histiocytes
- On the inner aspect of the capsule, the infiltrate shows a dense aggregation of eosinophils and neutrophils
- A delicate double layered membrane within the capsule consists of an outer acellular hyaline eosinophilic layer and an inner sparsely cellular layer
- This membrane can be readily separated from the capsule because of its loose attachment to the capsule
- This membrane contains the cyst as also the larval form of *T. solium*
- At cephalic extremity of the larva, the scolex with the rostellum, bothria (suckers) and hooklets may be identified.

Management

1. It is harmless to the oral tissues.
2. Over a period of time, localization in the brain, heart valves and orbit may produce important functional derangements.
3. Death of the parasite may occur after many years resulting in a granulomatous reaction around the parasite which then calcifies.

CYSTS OF SALIVARY GLANDS

MUCOCELES (FIG. 6.31)

Mucous extravasation cysts and mucous retention cysts are often referred to collectively as mucoceles. Generally, the term 'mucous extravasation cyst' is reserved for those lesions in which mucous has extravasated into the connective tissues and in which there is no epithelial lining. And the term 'mucous

retention cyst' is employed to describe mucocèles that result from dilatation of the ducts and which are lined by epithelium.

It is mainly classified as:

- Mucous extravasation cysts
- Mucous retention cysts.

Pathogenesis

- Obstruction of salivary gland duct due to a stone or some other cause may lead to dilatation of the duct proximal to the obstruction and results in formation of retention cyst lined by epithelium.
- Trauma to the duct or secretory acini may lead to extravasation of mucus in the connective tissue resulting in formation of mucus extravasation cyst.

Clinical Features

- **Harrison, 1975**, reviewed 400 cases from literature and reported that mucous extravasation cysts most commonly occur in adolescents and children, whereas, mucous retention cysts most commonly occur in adults⁴⁹
- In one study on 151 South African patients, the youngest patient found was 8 months old
- **Standish and Shafer, 1959**, reported a case of this lesion present at birth⁵⁰
- **Poker and Hopper, 1990**, reported a case of such a lesion occurring in the tongue of a 10-week-old girl⁵¹
- **Cataldo and Mosadomi, 1970**, in their study of 594 cases reported the occurrence of this lesion in only 2.7 percent of infants less than 1-year-old⁵²
- Most of the lesions occur as a round or oval, smooth and fluctuant swelling of the lower lip, followed by floor of the mouth, tongue, palate, buccal mucosa and upper lip.
- Superficial lesions appear bluish in color whereas, deep lesions appear as normal mucosa.



FIGURE 6.31: Mucocèle on lower lip

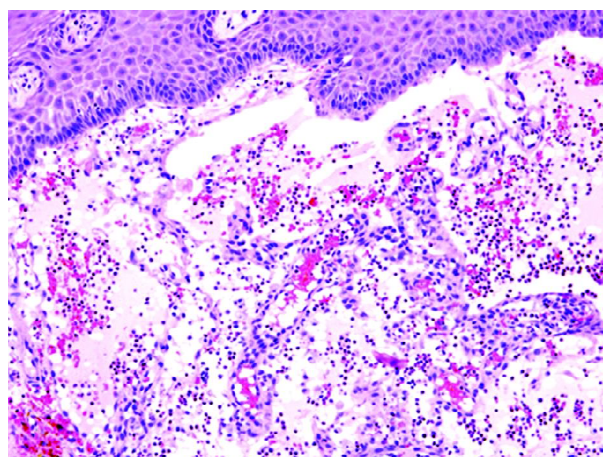


FIGURE 6.32: Histopathologic picture of mucocèle showing a lining of stratified squamous epithelium and underlying connective tissue with eosinophilic mucinous material surrounded by inflammatory cell infiltrate

HISTOPATHOLOGIC FEATURES (FIG. 6.32)

- **Robinson and Hjørtting-Hansen, 1964**, defined three distinct patterns of mucocèles⁵³
- Mucus extravasation cysts show two patterns, one which consists of numerous irregular pools of eosinophilic mucinous material and vacuolated macrophages termed as 'mucinophages', these were termed as poorly defined cysts. Others termed as well-defined cysts were further divided into two groups and differed only in that the periphery of one consisted of granulation tissue and was infiltrated by vacuolated macrophages, lymphocytes, eosinophils, etc.
- Mucous retention group was partially or completely lined by epithelium that was either flattened consisting of one or two layers of cells of stratified squamous epithelium.

Management

1. Mucocèles of smaller size require no specific treatment.
2. Larger lesions require surgical removal along with the removal of associated lobule of the salivary gland involved.

RANULA

The term ranula is used to describe mucocèles occurring on the floor of mouth.

Classification

They are of two types: superficial and plunging.

1. Superficial type develops as an extravasation or retention type mostly associated with trauma to one or more excretory ducts of submandibular or sublingual salivary glands
2. Plunging ranulas are a result of extravasation of sublingual glands, which ramify diffusely into the neck (Figs 6.33 and 6.34).



FIGURE 6.33: Ranula in the floor of mouth

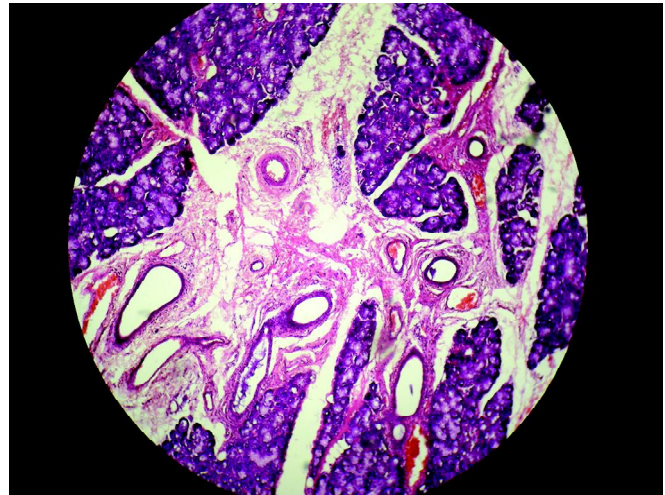


FIGURE 6.35: Histopathologic picture of a ranula showing a huge collection of mixed salivary gland acini. The connective tissue separating the lobules is delicate, loosely arranged with numerous mature and immature blood vessels. There is also a huge collection of mucoid material

Clinical Features

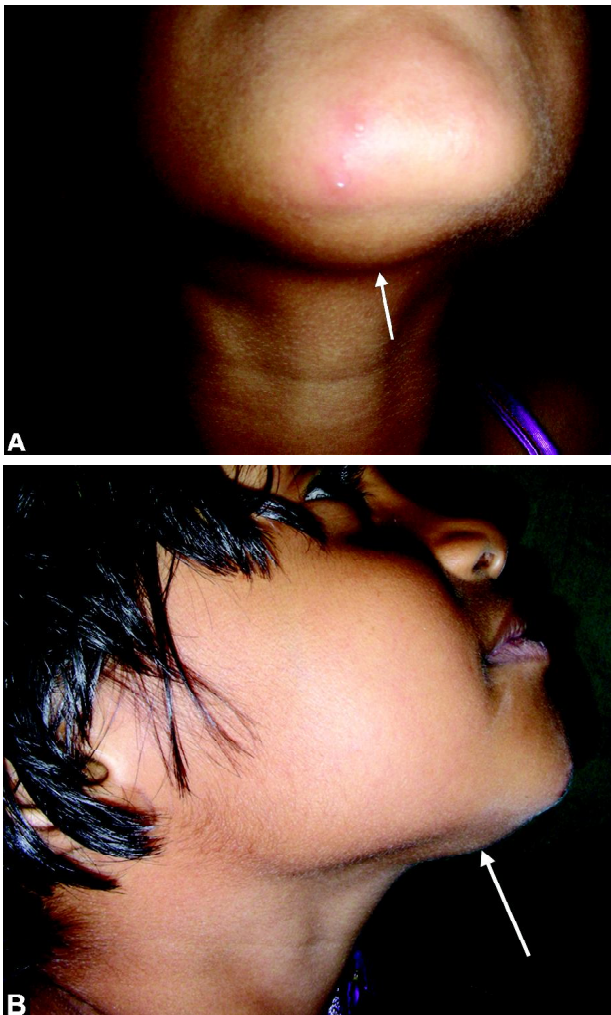
- They are mostly found associated with submandibular or sublingual glands
- They are usually unilateral
- Incidence in children and young adults is more common
- Occurrence in the floor of the mouth is common, where they appear translucent blue in color, that resembles a frog's belly, hence the name
- They are small fluctuant swellings
- Larger lesions may lift the tongue and cause difficulty in swallowing and speech
- The swelling increases in size during meals due to increased secretory activity as a part of gustatory stimulation
- Herniated projections of sublingual gland as a result of hiatus or deficiency between anterior and posterior parts of mylohyoid muscle had been reported as etiological factors for plunging ranulas.

Histopathologic features (Fig. 6.35)

- Histopathological features are same as mucocèles
- Majority of ranulas show lack of epithelial lining.

Management

1. Surgical removal of sublingual salivary gland.
2. **Rho et al, 2006**, proposed the use of a sclerosing and immune system stimulating agent OK-432. This agent is prepared from lyophilized *Streptococcus pyogenes*.⁵⁴



FIGURES 6.34A and B: Plunging ranula (arrows)

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Odontogenic Tumors in Children

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CHAPTER OVERVIEW

Introduction
Classification
Solid/multicystic ameloblastoma
Adenomatoid odontogenic tumor
Calcifying epithelial odontogenic tumor
Squamous odontogenic tumor
Ameloblastic fibroma
Ameloblastic fibrodentinoma
Ameloblastic fibro-odontoma
Complex odontoma

Compound odontoma
Odontoameloblastoma
Calcifying cystic odontogenic tumor
Dentinogenic ghost cell tumor
Odontogenic fibromas (epithelium poor and epithelium rich)
Odontogenic myxoma/fibromyxoma
Metastasizing ameloblastoma
Ameloblastic carcinoma
Primary intraosseous squamous cell carcinoma
Ameloblastic fibrosarcoma

INTRODUCTION

Odontogenic tumors are lesions derived from epithelial or ectomesenchymal tissues or both, which are part of the tooth-forming apparatus. They usually comprise of about one percent of all jaw tumors. Before proceeding towards various odontogenic tumors, a basic understanding of the histogenesis of the tooth and a clear difference between a tumor and hamartoma is necessary.

Tooth development begins when the dental lamina projects into the underlying ectomesenchyme. The cells of dental lamina differentiate into a layered cap with an inner and outer enamel epithelium, which contain the inner stratum intermedium and stellate reticulum layers. Changes also occur in the underlying ectomesenchyme forming the dental follicle and dental papilla. Mesenchymally derived odontoblasts form along the dental papilla and secrete dentin, which induces the inner enamel epithelium to become ameloblasts. Ameloblasts are responsible for enamel production and eventual crown formation. Cementoblasts and fibroblasts from the dental follicle mesenchyme deposit cementum on the root surface and form the periodontal membrane, respectively. The penetration of these cells through Hertwig's sheath at the edge of the enamel organ gives rise to epithelial rests of Malassez within the

periodontal ligament. The enamel organ then involutes to a monolayer, which becomes squamoid and ultimately fuses with the gingiva during eruption.

Any aberration from this normal process of tooth formation may either give rise to a cyst or a tumor formation. This chapter focuses on the most common odontogenic tumors occurring in children. Few lesions though being rare fall in the pediatric age group and thus are also discussed here.

DIFFERENCE BETWEEN A TUMOR AND A HAMARTOMA

- **Tumor:** A group of heterogeneous lesions that range from hamartomatous or non-neoplastic tissue proliferations to malignant neoplasms with metastatic capabilities.
- **Hamartoma:** Tumor like malformation, developmental in origin, with the tissue being native to the site.

CLASSIFICATION

- Odontogenic tumors are lesions derived from epithelial, ectomesenchymal and/or mesenchymal elements that are or have been a part of the tooth forming apparatus.
- French physician **Broca, 1867**, first proposed a classification of tumors originating from dental tissues.

- In 1992, WHO revised the classification of odontogenic tumors. The current classification was approved at a consensus conference held at Lyon (France) in July 2003.

DIFFERENCE BETWEEN WHO CLASSIFICATION AND THE CURRENTLY ACCEPTED CLASSIFICATION

- **Adenomatoid odontogenic tumor** is included in the group of tumors with odontogenic epithelium with mature, fibrous stroma: odontogenic ectomesenchyme not present (previously it was placed in group odontogenic epithelium with odontogenic ectomesenchyme with or without dental hard tissue formation).
- **Odontogenic keratocyst** (Keratinizing cystic odontogenic tumor) is also included in the group of tumors with odontogenic epithelium with mature, fibrous stroma: odontogenic ectomesenchyme not present.
- **Clear cell odontogenic tumor** which was included in the group of tumors with odontogenic epithelium with mature, fibrous stroma: odontogenic ectomesenchyme not present

is now included in malignant group of odontogenic carcinomas.

BENIGN

SOLID/MULTICYSTIC AMELOBLASTOMA

French physician Broca, 1868, first gave a detailed description of solid multicystic ameloblastoma.¹ **Malassez, 1884-85**, described it as epithelioma adamantin.^{2,3} **Churchill, 1934**, first gave the term “Ameloblastoma”.⁴ Adamantinoma is a misnomer as cells of tumor islands are not true ameloblasts.

Robinson defined ameloblastoma as “Usually unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent”.⁵

Etiology

The following etiological factors have been implicated:

- Irritation
- Infection
- Trauma

WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF ODONTOGENIC TUMORS (1992)

BENIGN

1. Odontogenic Epithelium without Odontogenic Ectomesenchyme:

- Ameloblastoma
- Squamous odontogenic tumor
- Calcifying epithelial odontogenic tumor (Pindborg's tumor)
- Clear cell odontogenic tumor

2. Odontogenic Epithelium with Odontogenic Ectomesenchyme, with or without Dental Hard Tissue Formation:

- Ameloblastic fibroma
- Ameloblastic fibro-dentinoma and Ameloblastic fibro-odontoma
- Odontoameloblastoma
- Adenomatoid odontogenic tumor
- Calcifying odontogenic cyst
- Complex and compound odontoma

3. Odontogenic Ectomesenchyme, with or without Included Odontogenic Epithelium:

- Odontogenic fibroma
- Myxoma (Odontogenic myxoma, myxofibroma)
- Benign cementoblastoma

MALIGNANT

1. Odontogenic Carcinomas

- Malignant ameloblastoma
- Primary intra-osseous carcinoma
- Malignant variants of other odontogenic tumors
- Malignant changes in odontogenic cysts

2. Odontogenic Sarcomas

- Ameloblastic fibrosarcoma (ameloblastic sarcoma)
- Ameloblastic fibro-dentinosa sarcoma and ameloblastic fibro-odontosarcoma

3. Odontogenic Carcinosarcoma

CURRENT CLASSIFICATION OF ODONTOGENIC TUMORS (JULY 2003)**A. NEOPLASMS AND TUMOR-LIKE LESIONS ARISING FROM ODONTOGENIC APPARATUS****BENIGN****1. Odontogenic epithelium with mature, fibrous stroma: odontogenic ectomesenchyme not present**

- Ameloblastomas
 - Solid/multicystic
 - Extraosseous/peripheral
 - Desmoplastic
 - Unicystic
- Adenomatoid odontogenic tumor
- Calcifying epithelial odontogenic tumor
- Squamous odontogenic tumor
- Keratinizing cystic odontogenic tumor

2. Odontogenic epithelium with odontogenic ectomesenchyme with or without dental hard tissue formation

- Ameloblastic fibroma
- Ameloblastic fibrodentinoma
- Ameloblastic fibro-odontoma
- Complex odontoma
- Compound odontoma
- Odontoameloblastoma
- Calcifying cystic odontogenic tumor
- Dentinogenic ghost cell tumor

3. Mesenchyme and/or odontogenic ectomesenchyme with or without included odontogenic epithelium

- Odontogenic fibromas (epithelium poor and epithelium rich)
- Odontogenic myxoma/fibromyxoma
- Cementoblastoma

MALIGNANT**1. Odontogenic carcinomas**

- Metastasizing malignant ameloblastoma
- Ameloblastic carcinoma
 - Primary
 - Secondary (dedifferentiated), intraosseous
 - Secondary (dedifferentiated), extraosseous
- Primary intraosseous squamous cell carcinoma (PIOSCC)
 - PIOSCC solid type
 - PIOSCC derived from odontogenic cysts
 - PIOSCC derived from keratinizing cystic odontogenic tumor
- Clear cell odontogenic carcinoma
- Ghost cell odontogenic carcinoma

2. Odontogenic sarcomas

- Ameloblastic fibrosarcoma
- Ameloblastic fibrodentinosa sarcoma

B. NEOPLASMS AND OTHER LESIONS IN THE MAXILLOFACIAL SKELETON**OSSEOUS NEOPLASMS**

Ossifying fibroma

NON-NEOPLASTIC LESIONS

- Fibrous dysplasia
- Osseous dysplasia
- Central giant cell lesion
- Cherubism
- Aneurysmal bone cyst
- Simple bone cyst

- Dietary deficiency
- Virus.

Pathogenesis

- Most solid/multicystic ameloblastomas occur as growths arising from remnants of odontogenic epithelium, more specifically rests of the dental lamina
- As early as 1885, **Malassez** suggested that intraosseous ameloblastomas may originate from “les debris épithéliaux” (cell rests of Malassez)³
- May arise as a result of neoplastic changes in the lining of odontogenic cysts (OKC, dentigerous cyst)
- May arise on odontomas
- Residues of dental lamina outside the bone may also give rise to ameloblastoma.

Types

Basically of four types:

1. Solid/Multicystic
2. Extraosseous/Peripheral
3. Desmoplastic
4. Unicystic.

SOLID/MULTICYSTIC

CLINICAL FEATURES

- Occurs in the age range of 4 to 92 years.
- Seen more often in males as compared to females.
- Occurrence in posterior mandibular area is common (Fig. 7.1).
- Painless slow growing lesion.
- Migration, loosening and root resorption may be seen.
- Paresthesia may be present.



FIGURE 7.1: Solid/multicystic ameloblastoma showing a swelling in the lower right posterior region of the jaw

- Expansion and erosion of cortical plates (egg shell crackling) may be evident
- Ameloblastomas in children differ from adults, with a higher percentage of unicystic tumors. African children appear to resemble the adult pattern.⁶

RADIOGRAPHIC FEATURES

- Multilocular radiolucent appearance.
- May be unilocular (Fig. 7.2).

Various Terminologies Radiographically Used

- **Soap bubble:** Consists of several circular compartments that vary in size and usually appear to overlap somewhat (Fig. 7.3)
- **Honeycomb:** Lesions whose compartments are small and tend to be quite uniform in size (Fig. 7.4)
- **Tennis racket:** Lesions composed of angular rather than rounded compartments that result from the development of more or less straight septae (Fig. 7.5).



FIGURE 7.2: Radiographic picture of solid/multicystic ameloblastoma showing a unilocular radiolucent expansile lesion in the lower right posterior region of the jaw

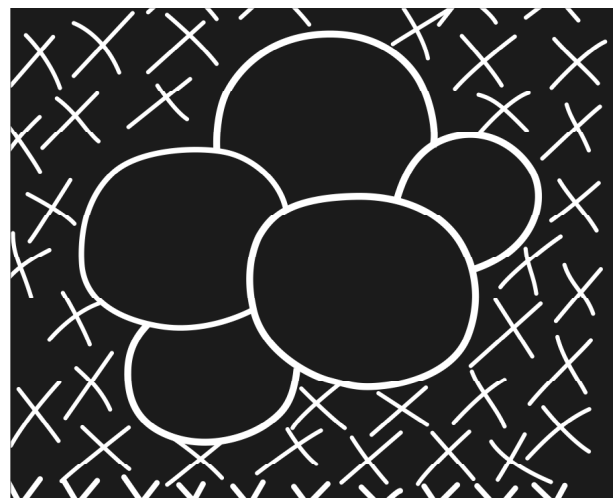


FIGURE 7.3: Diagrammatic representation of radiographic picture of soap bubble appearance

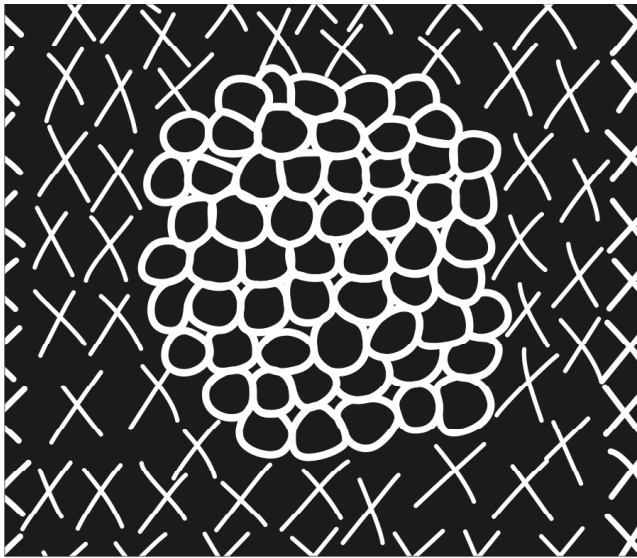


FIGURE 7.4: Diagrammatic representation of radiographic picture of honeycomb appearance

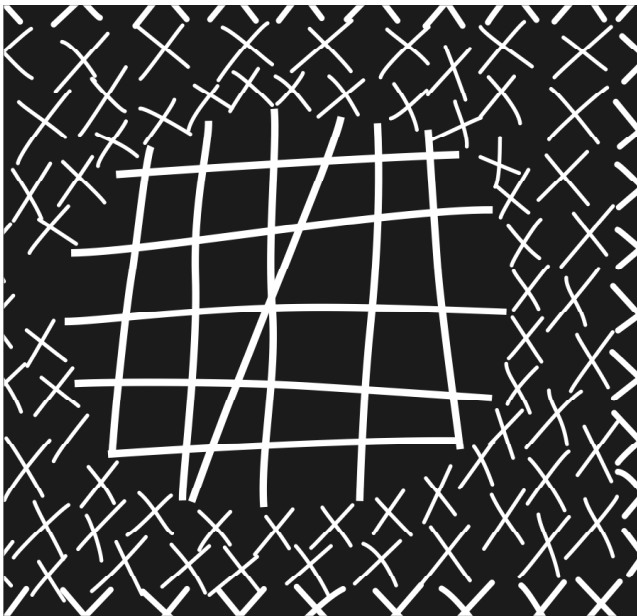
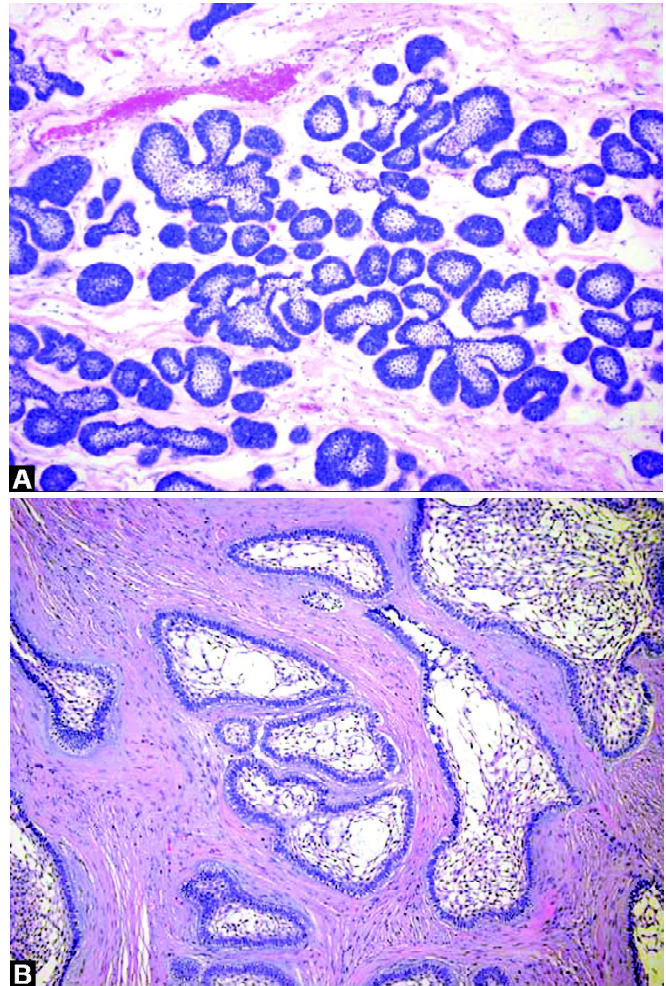


FIGURE 7.5: Diagrammatic representation of radiographic picture of tennis racket appearance

HISTOPATHOLOGIC FEATURES

Definition

Ameloblastoma may be defined as a polymorphic neoplasm consisting of proliferating odontogenic epithelium usually occurring in two main patterns. In follicular type of growth, tumor consists of enamel organ-like islands or follicles of epithelial cells, while in the plexiform type, the epithelium forms continuous anastomosing strands. In both types, epithelial components are embedded in mature connective tissue stroma.



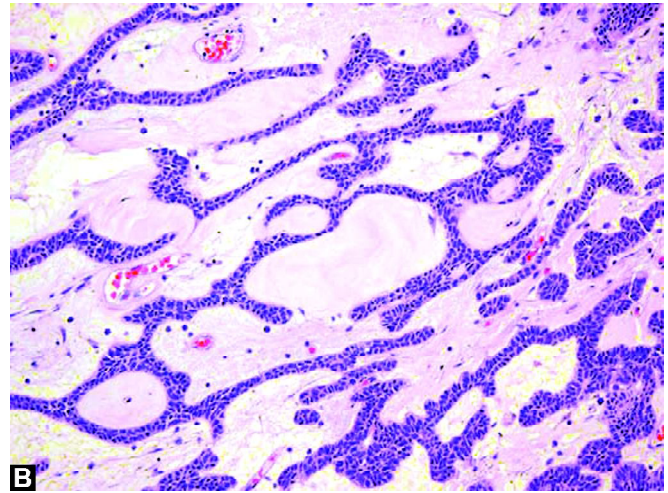
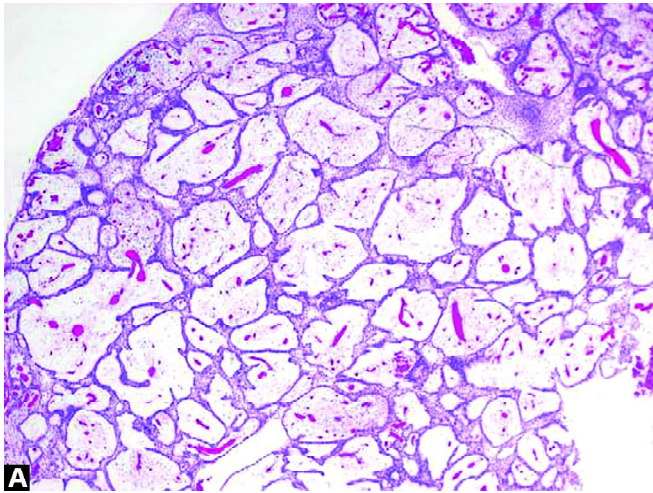
FIGURES 7.6A and B: Histopathologic picture of follicular ameloblastoma showing islands with central mass of polyhedral cells

Histopathological types of ameloblastomas

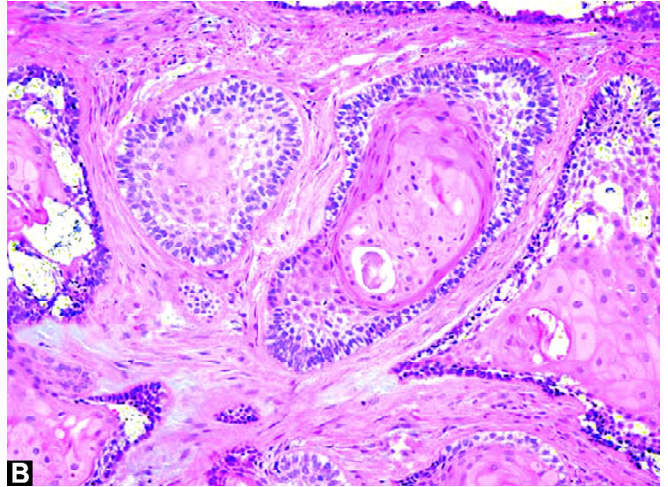
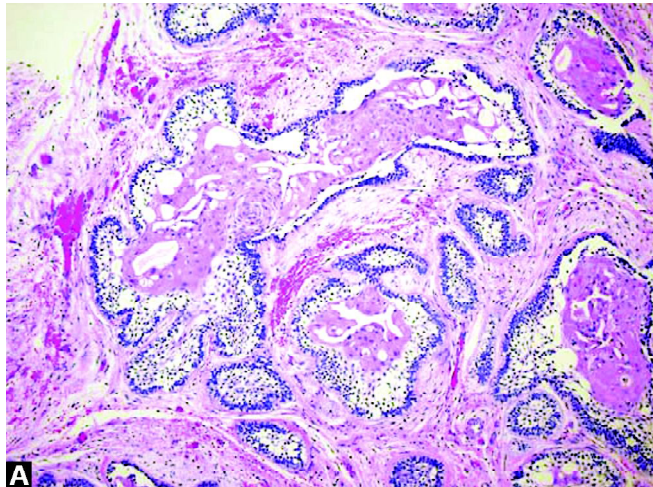
- Follicular
- Plexiform
- Acanthomatous
- Granular cell
- Desmoplastic
- Unicystic
- Basal cell
- Clear cell
- Keratoameloblastoma
- Hemangiomas.

Follicular ameloblastoma (Figs 7.6A and B)

- Islands with central mass of polyhedral cells
- Polyhedral cells resemble stellate reticulum
- Stellate reticulum surrounded by layer of cuboidal or columnar cells resembling preameloblasts.



FIGURES 7.7A and B: Histopathologic picture of plexiform ameloblastoma showing tumor epithelium arranged as a network



FIGURES 7.8A and B: Histopathologic picture of acanthomatous ameloblastoma showing tumor islands with extensive squamous metaplasia

Plexiform ameloblastoma (Figs 7.7A and B)

- Central mass of polyhedral cells resembles stellate reticulum
- Tumor epithelium is arranged as a network
- Network is bound by a layer of cuboidal or columnar cells resembling preameloblasts.

Acanthomatous ameloblastoma (Figs 7.8A and B)

- It is a variant of ameloblastoma
- Tumor islands consist of extensive squamous metaplasia
- Sometimes keratin formation is seen within the islands
- Keratin pearls may become calcified.

Granular cell ameloblastoma (Fig. 7.9)

- It is similar to the follicular type; shows extensive granular transformation of stellate reticulum like cells
- Granular cells may be cuboidal, columnar or rounded with cytoplasm showing acidophilic granules

- Acidophilic granules are usually lysosomal aggregates
- Immunohistochemical studies indicate that granularity may be due to increased apoptosis and associated phagocytosis by neighbouring neoplastic cells.

Basal cell ameloblastoma (Fig. 7.10)

- Basal cell ameloblastoma is rarely seen
- Most actively proliferating
- Most immature
- Predominantly basaloid pattern of cells is seen.

Clear cell ameloblastoma

May contain periodic-acid-Schiff (PAS) positive cells localized in stellate reticulum like cells.

Keratoameloblastoma and Papilliferous Keratoameloblastoma

- **Pindborg, 1970**, first stated that an ameloblastoma consisting partly of keratinizing cysts and partly of tumor

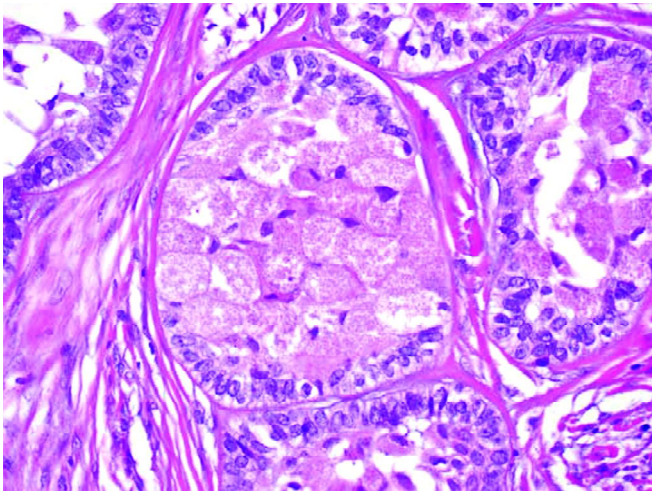


FIGURE 7.9: Histopathologic picture of granular cell ameloblastoma showing extensive granular transformation of stellate reticulum like cells

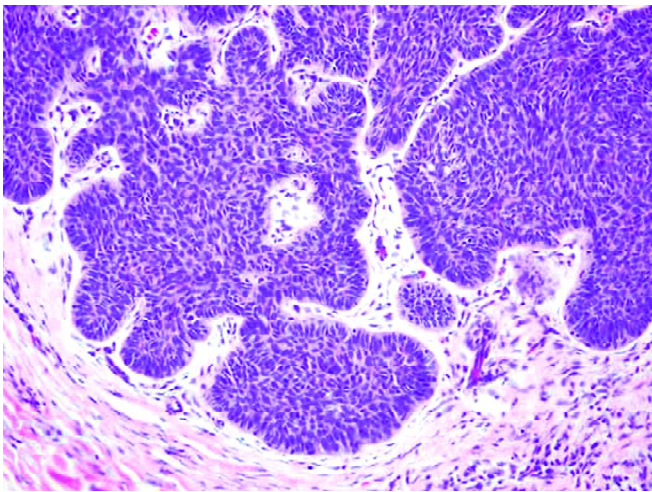


FIGURE 7.10: Histopathologic picture of basal cell ameloblastoma showing basaloid pattern of cells

islands with papilliferous appearance be called Papilliferous Keratoameloblastoma.⁷

- **Altini et al, 1991**, noted a similar tumor without papilliferous epithelium and extensive necrosis in the middle of the follicle.⁸

Hemangiomatous ameloblastoma

- **Kuhn, 1932**, called hemangiomatous ameloblastoma as an ameloblastoma in which, part of the tumor contains spaces filled with blood or large endothelium lined capillaries.⁹
- **Origin of vascular component:**
 - Angiogenesis during tumor development and trauma from tooth extraction.

- Collision tumor: A stromal cyst in plexiform ameloblastoma, thus resulting in a secondary change.

Management

Radical surgical intervention.

PERIPHERAL AMELOBLASTOMA

Peripheral ameloblastomas occur mostly in the soft tissues overlying the tooth-bearing areas and do not invade the underlying bone. **Stanley and Korgh, 1959**, were the first to report a completely documented case of this lesion.¹⁰

Pathogenesis

Peripheral ameloblastoma arises from two major sources:

1. Remnants of dental lamina located in the soft tissues overlying the tooth bearing areas of the jawbones.
2. Surface epithelium.

Clinical Features

- Painless, sessile, firm, exophytic growth
- Surface may be smooth or granular, normal in color or slightly red
- Occurs in the age range of 9 to 92 years
- Males are more commonly affected than females
- Mandibular premolar areas are most often affected than maxilla, and in maxilla, tuberosity area is most often involved.

Radiographic Features

Since it is a superficial lesion, there is no involvement of bone but, there may be cupping or saucerization of the bone due to pressure resorption.

Histopathologic Features

- Similar features as compared to solid/multicystic ameloblastoma but the tumor is seen peripherally.
- Palisading, cuboidal/columnar peripheral cells.
- Central polyhedral cells resemble stellate reticulum.
- Stroma is of mature connective tissue.

Management

1. Peripheral ameloblastomas require conservative suprapariosteal surgical excision.
2. Good results can be achieved in the treatment of ameloblastoma in children using conservative surgery. In the event of recurrence, a second surgery can be successful. Patient compliance and careful follow-up are important.¹¹

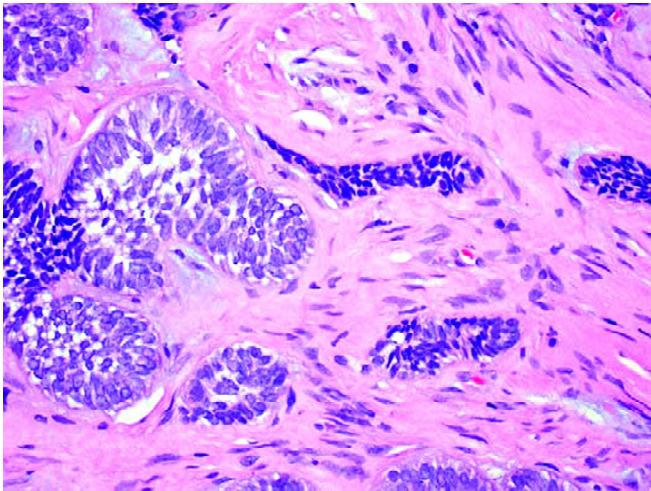


FIGURE 7.11: Histopathologic picture of desmoplastic ameloblastoma showing bizarrely shaped islands and cords of odontogenic epithelium of varying sizes embedded in a desmoplastic connective tissue stroma

DESMOPLASTIC AMELOBLASTOMA

Eversole and coworkers, 1984, are usually credited for the first English language publication on the desmoplastic ameloblastoma.¹² This tumor is characterized by an unusual histomorphology, including extensive stromal collagenization or desmoplasia, leading to the proposed term ameloblastoma with pronounced desmoplasia or desmoplastic ameloblastoma.

Pathogenesis

Presence of oxytalan fibers in the stromal tissue indicates that the tumor is derived from epithelial rests of Malassez in periodontal membrane.

Clinical Features

- Variant of solid/multicystic ameloblastoma
- Occurs in age range of 17 to 72 years
- Males are affected more as compared to females
- Occurs with equal distribution in maxilla and mandible
- Presents as a painless swelling.

Radiographic Features

Unilocular or multilocular radiolucency with ill-defined borders.

Histopathologic Features (Fig. 7.11)

- Benign invasive variant of solid/multicystic ameloblastoma consisting of proliferating, irregular, bizarre shaped islands and cords of odontogenic epithelium of varying sizes embedded in a desmoplastic connective tissue stroma.



FIGURE 7.12: Unicystic ameloblastoma showing an ulcerated lesion in the lower left posterior region of the jaw

- A possible “transitional” form of desmoplastic ameloblastoma, showing microscopic features of the desmoplastic variant together with areas typical of “classic” follicular or plexiform ameloblastoma, has been called a “hybrid” lesion of ameloblastoma.

UNICYSTIC AMELOBLASTOMA

Robinson and Martinez, 1977, introduced the term unicystic ameloblastoma.¹³ The term unicystic is derived from the macro- and micro-scopic appearance, the lesion being essentially a well-defined, often large monocystic cavity with a lining, focally but rarely entirely composed of odontogenic (ameloblastomatous) epithelium.

Types

Basically of two types:

1. Those associated with unerupted tooth (dentigerous variant)
2. Those lacking association with unerupted tooth (non-dentigerous variant).

Clinical Features (Fig. 7.12)

- Dentigerous variant occurs in younger age group. Almost 78.3% of cases occur in the first two decades as compared to non-dentigerous variant in which, 29.4% of cases occur in the first two decades
- Males are affected more as compared to females
- Occurrence in mandible is more as compared to females.



FIGURE 7.13: Radiographic picture of unicystic ameloblastoma showing a unilocular radiolucent lesion with resorption of root

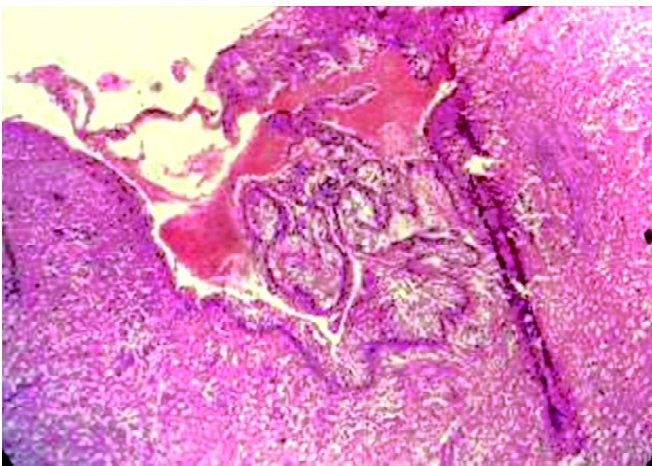


FIGURE 7.14: Histopathologic picture of unicystic ameloblastoma showing a large monocystic cavity with a lining composed of odontogenic (ameloblastomatous) epithelium

Radiographic Features (Fig. 7.13)

- Either unilocular or multilocular radiolucency
- Unilocular pattern is commonly seen in dentigerous variant, and non-dentigerous variant shows either unilocular or multilocular pattern.

Histopathologic Features

- Well-defined, large monocystic cavity with a lining composed of odontogenic (ameloblastomatous) epithelium (Fig. 7.14).

- *WHO classification, 1992: (histopathological classification)*

Subgroup	Interpretation
1	Luminal
1.2	Luminal and Intraluminal
1.2.3	Luminal, intraluminal, intramural
1.3	Luminal and intramural

Unicystic ameloblastoma group 1.2 (luminal and intraluminal) is sometimes referred to as plexiform unicystic ameloblastoma.

Management

1. Conservative treatment for group 1 and 1.2
2. Aggressive management for group 1.2.3 and 1.3

ADENOMATOID ODONTOGENIC TUMOR

Unal and coworkers quoted that, Steensland, 1905, in his report for the first time coined the term epithelioma adamantinum for this lesion.¹⁴ Finally, Philipsen and Birn, 1969, termed this lesion as adenomatoid odontogenic tumor.¹⁵ Few consider it to be a hamartomatous lesion, while few perceive it as a benign embryonal neoplasm. The current classification groups it into odontogenic tumor with odontogenic epithelium with mature stroma without ectomesenchyme.

Classification

Two Types

1. Intraosseous
 - Follicular
 - Extrafollicular
2. Extraosseous.

Pathogenesis

May arise from:

- Rests of dental lamina
- Enamel organ.

Clinical Features

- Occurs in the age range of 3 to 87 years
- More commonly seen in females as compared to males
- Follicular variant is three times more frequently seen than the extrafollicular variant
- Occurrence in maxilla is more common than mandible
- Maxillary canine region accounts for 40% of adenomatoid odontogenic tumors (Fig. 7.15)
- Extraosseous variant is common in maxillary anterior gingival region
- Usually it is roughly spherical with well-defined fibrous capsule



FIGURE 7.15: Adenomatoid odontogenic tumor presenting as a swelling in upper right anterior region of the jaw

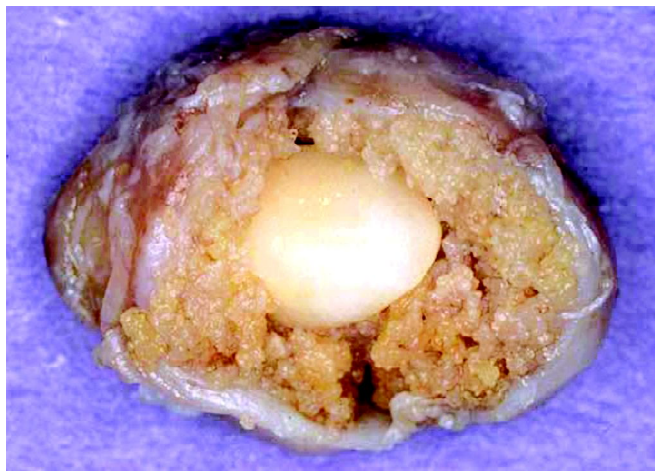


FIGURE 7.16: Specimen of adenomatoid odontogenic tumor showing a solid tumor mass with large cystic spaces containing yellowish semisolid material

- Cut surface shows a solid tumor mass with large cystic spaces containing yellowish semisolid material (Fig. 7.16)
- Peripheral variant shows epulis like growth attached to palatal or labial gingiva.

Radiographic Features

- Follicular: Well-defined unilocular radiolucency associated with crown or part of root of the tooth (Fig. 7.17)
- Extrafollicular: Not associated with tooth. Well-defined, unilocular radiolucency between, above or superimposed on tooth roots
- Peripheral variant: Saucerization of bone.

Histopathologic Features

- Ameloblast like cells are arranged in sheets or strands or form a rosette pattern



FIGURE 7.17: Radiographic picture of adenomatoid odontogenic tumor showing a unilocular radiolucency associated with the crown of canine

- Characteristic feature is duct-like arrangement of ameloblast like cells (Fig. 7.18)
- Nuclei of cells face away from the center
- Central space may contain eosinophilic material (eosinophilic coagulum)
- Foci of calcification may be scattered throughout the tumor
- Connective tissue is scanty.

May be associated with the following lesions:

- Dentigerous cyst
- Calcifying epithelial odontogenic tumor
- Odontoma
- Ameloblastoma
- Calcifying odontogenic cyst.

Management

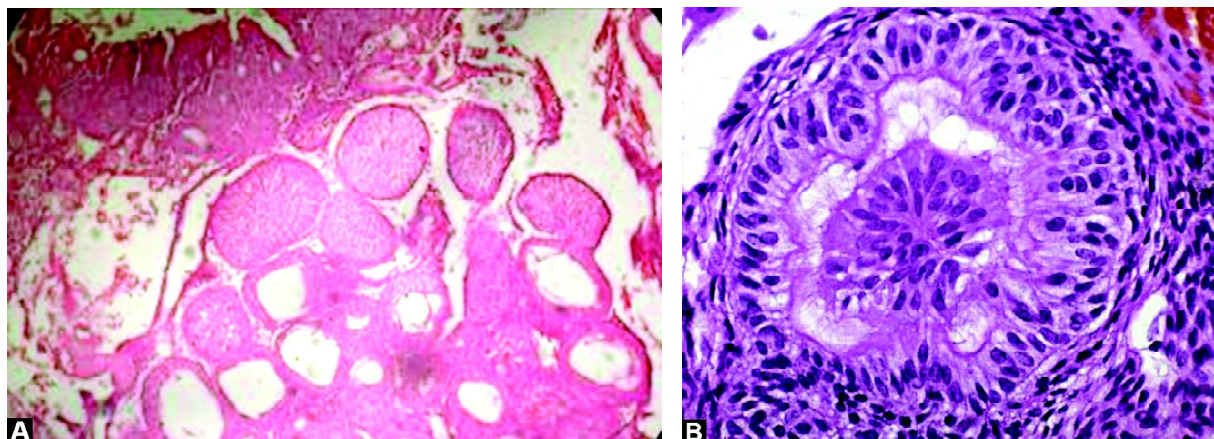
1. Surgical enucleation is the treatment of choice.
2. Curettage.

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR

Initially was called as calcifying ameloblastoma, malignant odontoma, etc. Then **Pindborg, 1955**, coined the term 'Calcifying epithelial odontogenic tumor'.¹⁶ Hence, also referred to as Pindborg's tumor. This term has also been accepted by WHO.

Pathogenesis

- May arise from reduced enamel epithelium of unerupted tooth



FIGURES 7.18A and B: Histopathologic picture of adenomatoid odontogenic tumor showing a duct-like arrangement of ameloblast like cells



FIGURE 7.19: Calcifying epithelial odontogenic tumor presenting as a swelling in the lower left posterior region of the jaw

- Peripheral variant may arise from:
 - Rests of dental lamina
 - Basal cells of oral epithelium.

Clinical features

- It is a benign neoplasm located intraosseously and extra-osseously
- Occurs in the age range of 8 to 92 years
- Males are affected more commonly than females
- Occurs more commonly in mandibular premolar-molar area as compared to maxilla (Fig. 7.19)
- Intraosseously, it appears as a painless mass with slow growth
- In the maxilla, nasal congestion, epistaxis and headache are common symptoms
- Extraosseously, it appears as a painless, firm mass on gingival tissue.



FIGURE 7.20: Radiographic picture of calcifying epithelial odontogenic tumor showing a multilocular radiolucent area containing radiopaque masses of varying sizes and opacities

Radiographic Features

Irregular unilocular or multilocular radiolucent area containing radiopaque masses of varying sizes and opacities (Fig. 7.20).

Histopathologic Features

- Tumor composed of sheets or islands of polyhedral odontogenic epithelial cells.
- Cells have a prominent cellular outline and intercellular bridges.
- Nuclei show variations in shape and size.
- Epithelial component encloses homogenous, eosinophilic amyloid-like material.
- Calcified concentric rings may be seen intraepithelially called as “Liesegang rings” (Fig. 7.21).
- Connective tissue is fibrous in nature.

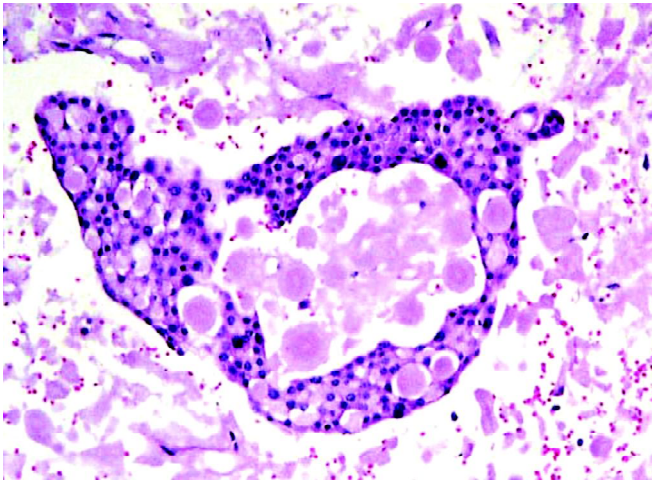


FIGURE 7.21: Histopathologic picture of calcifying epithelial odontogenic tumor showing sheets or islands of polyhedral odontogenic epithelial cells. Presence of "Liesegang rings" can be appreciated within the epithelium



FIGURE 7.22: Squamous odontogenic tumor presenting as an incisor-canine gingival mucosal ulceration and labial infiltration

Management

1. Small intrabony lesions with well defined borders are treated with enucleation or curettage followed by removal of a thin layer of bone adjacent to the tumor.
2. Recurrent tumors require segmental resections or hemimandibulectomy or hemimaxillectomy.

SQUAMOUS ODONTOGENIC TUMOR (FIG. 7.22)

Pullon et al, 1975, first coined the term squamous odontogenic tumor for this lesion located in the periodontium.¹⁷ It is a benign but locally infiltrative odontogenic neoplasm.

Pathogenesis

- Controversial
- May arise from epithelial rests of Malassez in the periodontal ligament
- May be hamartomatous
- The peripheral variant may arise from gingival surface epithelium.

Clinical Features

- Occurs in the age range of 8 to 74 years
- Incidence in females is more as compared to males
- Occurrence in mandibular posterior region is more common as compared to maxilla
- The most common variant is the central type, peripheral variant is rare
- Swelling in alveolar process, mobility of teeth and pain are common signs and symptoms.

Radiographic Features

- Central variant shows well-defined radiolucency between roots of teeth
- May be unilocular or multilocular
- Peripheral variant shows saucerization of bone.

Histopathologic Features

- Islands of squamous epithelium are seen within mature connective tissue stroma (Fig. 7.23)

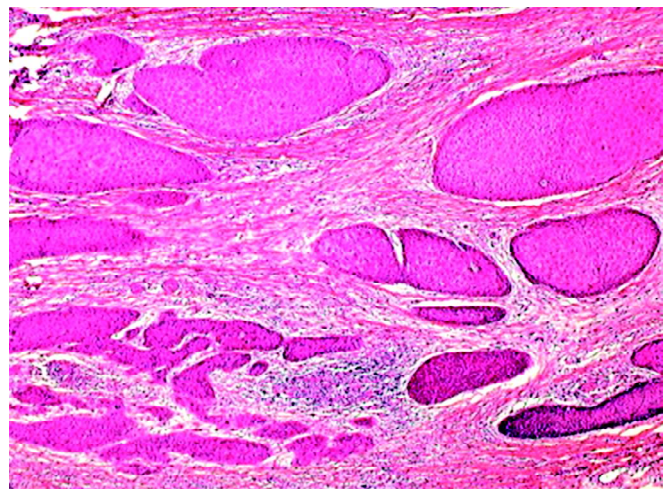


FIGURE 7.23: Histopathologic picture of squamous odontogenic tumor showing numerous islands of benign, well-differentiated, stratified, squamous epithelium in an abundant, mature, connective tissue stroma. Epithelial cells are without cytologic atypia and surrounded by fibrous tissue



FIGURE 7.24: Ameloblastic fibroma presenting as a swelling in the upper anterior region of the jaw

- Peripheral layer of cells are low cuboidal as compared to tall columnar cells seen in solid/multicystic ameloblastoma
- Few islands may show degeneration of spinous cells.

Management

1. Conservative surgical intervention
2. Curettage
3. Local excision
4. Aggressive lesions are treated by *en bloc* excision.

ODONTOGENIC EPITHELIUM WITH ODONTOGENIC ECTOMESENCHYME WITH OR WITHOUT DENTAL HARD TISSUE FORMATION

- Ameloblastic fibroma
- Ameloblastic fibrodentinoma
- Ameloblastic fibroodontoma
- Complex odontoma
- Compound odontoma
- Odontoameloblastoma
- Calcifying cystic odontogenic tumor
- Dentinogenic ghost cell tumor.

AMELOBLASTIC FIBROMA (FIG. 7.24)

Kruse, 1891, first coined the term ameloblastic fibroma.¹⁸ It is considered to be a true mixed tumor as both epithelial and ectomesenchymal components are neoplastic. Only in comparison with ameloblastic fibrodentinoma and ameloblastic fibroodontoma, dental hard tissue formation is not seen.

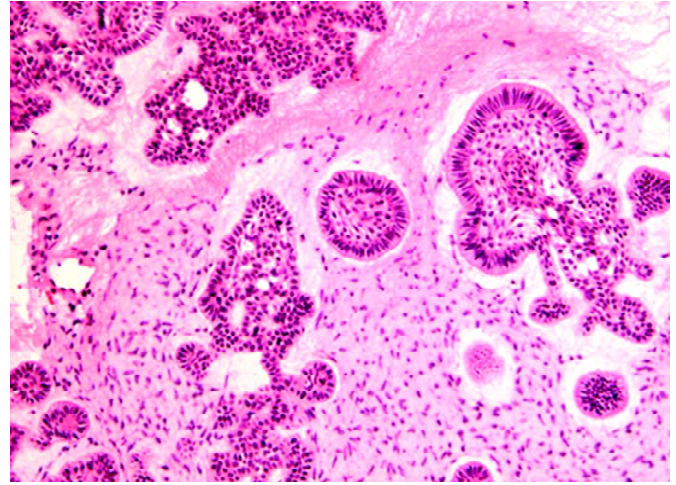


FIGURE 7.25: Histopathologic picture of ameloblastic fibroma showing islands of odontogenic epithelium within the ectomesenchyme

Pathogenesis

- Ameloblastic fibroma is a neoplasm of odontogenic origin with epithelial and ectomesenchymal components
- Morphologically, ameloblastic fibroma is similar to the normal tooth anlage before hard tissue formation has started
- Pathogenetically, the epithelial components—the ameloblast-like cells are too primitive to induce the cells of the ectomesenchyme for odontoblast differentiation. The step of induction of odontoblastic differentiation is lacking in ameloblastic fibroma.

Clinical Features

- Occurs in first and second decade of life.
- Painless, slow growing, expansile lesion.
- Males are more commonly affected as compared to females.
- Posterior mandible is affected more often than maxilla.

Radiographic Features

Well-defined uni- or multilocular radiolucency with a radiopaque border.

Histopathologic Features (Fig. 7.25)

- Irregular strands, islands or cords of odontogenic epithelium
- Peripheral row of tall columnar cells resembling ameloblasts.
- Center of ameloblast-like cells show cells resembling stellate reticulum

- Ectomesenchymal cells show loose, delicate collagen fibers
- Sometimes myxomatous area may be seen within the ectomesenchyme.

Management

1. Surgical resection.
2. Mosby et al, 1998, suggest the conservative removal of ameloblastic fibroma and modified block resection to prevent any recurrence.¹⁹

AMELOBLASTIC FIBRODENTINOMA

Straith, 1936, first coined the term ameloblastic fibrodentinoma.²⁰ He defined ameloblastic fibrodentinoma as a very rare neoplasm composed of odontogenic epithelium and immature connective tissue and characterized by the formation of dysplastic dentin.

Pathogenesis

- Ameloblastic fibrodentinoma is of odontogenic origin with epithelial and ectomesenchymal components
- Considered to be one of the intermediate stages between ameloblastic fibroma and ameloblastic fibrodentinoma.

Clinical Features

- Occurs in first and second decade of life. Most of the cases are diagnosed before the age of 20 years
- Painless, slow growing tumor
- May be associated with unerupted teeth.

Radiographic Features

Well-defined uni- or multilocular radiolucency with radiopacities.

Histopathologic Features (Fig. 7.26)

- Strands and islands of odontogenic epithelium in cell-rich primitive ectomesenchyme resembling dental papilla
- There are some inductive changes that lead to the formation of dentinoid.

Management

Surgical resection.

AMELOBLASTIC FIBRO-ODONTOMA

Hooker, 1967, first used the term 'ameloblastic odontoma' for ameloblastic fibro-odontoma.²¹ Later on various cases were reported in the literature and finally the term ameloblastic fibro-odontoma was agreed upon.

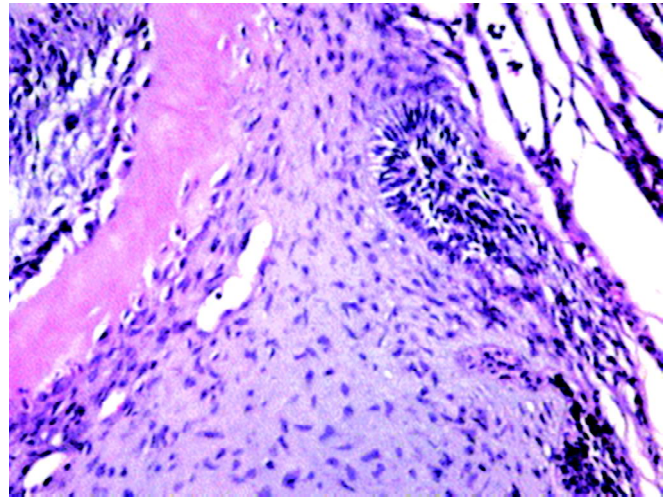


FIGURE 7.26: Histopathologic picture of ameloblastic fibrodentinoma showing an island of ameloblast-like cells embedded within a primitive dental papilla-like area

Pathogenesis

- Ameloblastic fibro-odontoma is a member of the family of mixed odontogenic tumors. It is of odontogenic origin with epithelial and ectomesenchymal components
- The inductive changes that lead to formation of enamel in addition to dentin are more advanced as compared to ameloblastic fibroma and ameloblastic fibrodentinoma.

Clinical Features

- It is basically described as the tumor of childhood and adolescence
- Occurs in the age range 1 to 22 years
- Males are affected more as compared to females
- Occurrence in mandibular posterior area is common
- Painless, slow growing, expansile lesion.

Radiographic Features (Fig. 7.27)

Well-defined uni- or multilocular radiolucency with a radiopaque border.

Histopathologic Features (Fig. 7.28)

- Irregular strands and islands of odontogenic epithelium within the ectomesenchymal tissue
- Center of the islands consists of enamel matrix, surrounded by dentin and cementum
- Epithelium appears ameloblast-like with few stellate reticulum cells.



FIGURE 7.27: Radiographic picture of ameloblastic fibro-odontoma showing a multilocular radiolucency with radiopaque border

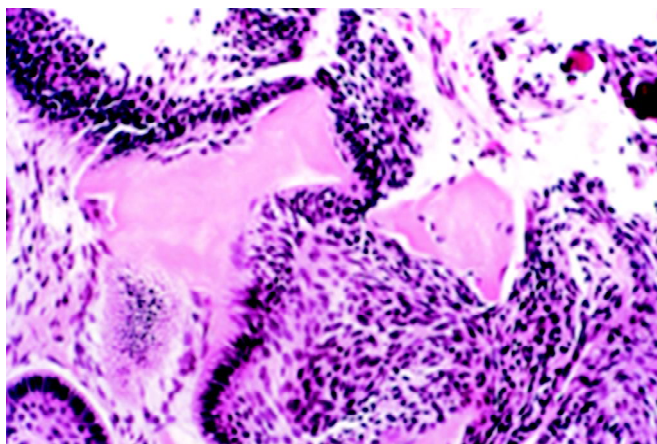


FIGURE 7.28: Histopathologic picture of ameloblastic fibro-odontoma showing irregular strands and islands of odontogenic epithelium within the ectomesenchymal tissue. Center of the islands consists of enamel matrix

Management

1. Depends on the nature of the lesion.
2. Conservative approach if lesion is not extensive.
3. Surgical resection if lesion is extensive.

ODONTOMA

Odontoma means a tumor of odontogenic origin. Yet, it comes under the category of mixed odontogenic tumors as it consists of both epithelial and ectomesenchymal components. Both epithelial and ectomesenchymal components appear normal morphologically but there is a deficit in structural arrangement. Thus few opine on it being a *hamartomatous lesion* than a true neoplasm. It is called as a composite odontoma as it is composed of more than one type of tissue.

Etiology

- Local trauma
- Infection
- Family history
- Genetic mutation.

Pathogenesis

It is a self-limiting developmental anomaly or hamartomatous malformation.

Two Types

1. Complex odontoma
2. Compound odontoma.

This is an arbitrary distinction because it is based on the appearance of tooth-like structures (compound) or mass of disorganized odontogenic tissues (complex).

Complex odontoma

Clinical features

- Occurs in the age range of 2 to 74 years
- Males are more commonly affected as compared to females
- Occurrence in the posterior mandible is most common followed by anterior maxilla
- It is a slow growing painless mass, expanding in nature.

Radiographic Features

Radiographically, it shows three stages based on the degree of mineralization:

1. *First stage:* Radiolucency due to lack of calcification is seen ("*weiches odontom*" = soft odontoma).
2. *Intermediate stage:* Partial calcification is seen.
3. *Third (Final) stage:* Radiopacity surrounded by a thin radiolucent line is seen (Fig. 7.29).

Histopathologic features

- Cementum or cementum-like material admixed with dentinoid substance, small spaces with pulp tissue, enamel matrix and epithelial remnants are generally observed (Fig. 7.30)
- In 16% of the cases, ghost cells are seen
- Ghost cells are eosinophilic altered epithelial cells characterized by the loss of nuclei with preservation of basic cellular outline
- It either represents coagulative necrosis or may be an aberrant keratinization of odontogenic epithelium.

Management

1. Conservative enucleation is recommended as the treatment of choice for complex odontomas.
2. **Blinder et al, 1993**, suggested an intraoral lingual approach for mandibular odontomas.²²



FIGURE 7.29: Radiographic picture of complex odontoma (arrow) showing the odontoma surrounded by a radiolucent periphery. There is retention of the deciduous canine

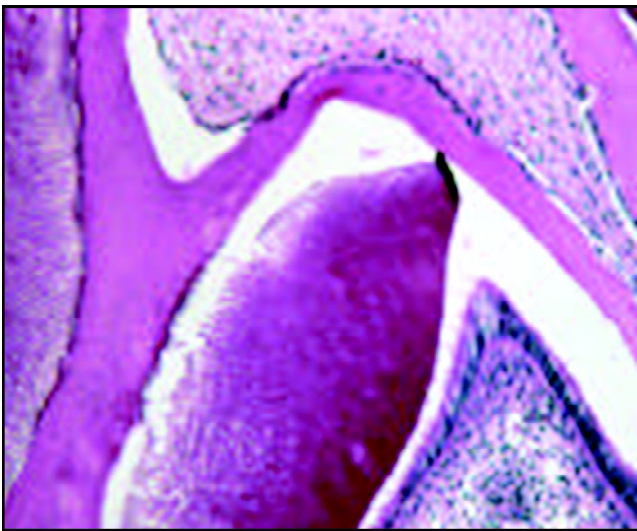


FIGURE 7.30: Histopathologic picture of complex odontoma showing enamel matrix and odontogenic epithelium

Compound odontoma

Pathogenesis

It is odontogenic in origin and may develop in the later stages of ameloblastic fibroma if left untreated.

Clinical features

- 75% of cases occur before the age of 20 years
- Males are affected more frequently than females
- Anterior maxilla is the most frequent location.



FIGURE 7.31: Radiographic picture of compound odontoma showing small radiopaque masses preventing eruption of the central incisor



FIGURE 7.32: Histopathologic picture of compound odontoma showing denticles embedded in fibrous stroma

Radiographic features

Radiopaque mass of varying size composed of a disorderly pattern of tooth-like structure (Fig. 7.31).

Histopathologic features

- Consists of dental tissues like enamel, dentin, cementum, pulp tissue with more or less regular arrangement (Fig. 7.32)
- Three percent of the cases consist of ghost cells.

Management

1. Conservative enucleation of the odontoma is the treatment of choice with care taken to see that all denticles have been removed, because some may be easily overlooked.
2. Unerupted neighboring teeth may be saved when the prognosis for tooth eruption is good.



FIGURE 7.33: Odontoameloblastoma presenting as a swelling in the alveolar bone of lower right anterior region

ODONTOAMELOBLASTOMA

Hooker, 1967,²¹ used the term ameloblastic odontoma for this lesion. Then *Thoma, 1970*, coined the term 'Odontoameloblastoma'.²³

Pathogenesis

Although clearly of odontogenic origin, its pathogenesis is not known.

Clinical features

- Occurs in the age range of 3 to 50 years
- Males are affected more as compared to females
- Occurrence in posterior mandible is more common as compared to maxilla
- It is an expansile, destructive lesion
- Presents with a swelling in alveolar bone (Fig. 7.33)
- Dull pain may be associated with the lesion
- Delayed eruption of teeth may be seen.

Radiographic features

Well-defined unilocular or multilocular radiolucency containing radiopaque masses.

Histopathologic features

- Odontoameloblastoma was defined by WHO, 1992, as a very rare neoplasm that includes odontogenic ectomesenchyme, in addition to odontogenic epithelium that resembles an ameloblastoma in both structure and behavior (Fig. 7.34)
- Irregular strands and islands of odontogenic epithelium may be seen within the ectomesenchymal tissue

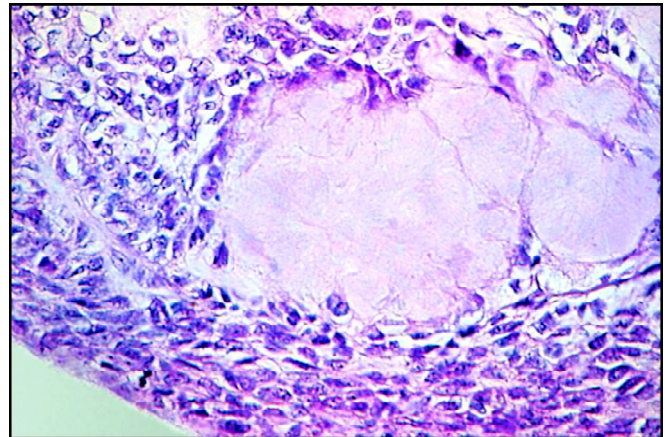


FIGURE 7.34: Histopathologic picture of odontoameloblastoma showing odontogenic epithelium within the ectomesenchymal tissue. Areas of dentinoid are evident

- Due to the presence of odontogenic ectomesenchyme, inductive changes take place forming dysplastic dentin and enamel that are arranged haphazardly
- Ghost cells may be present.

Management

Since these lesions are considered to be as aggressive as ameloblastoma, radical surgical intervention is the treatment of choice.

Note: Calcifying cystic odontogenic tumor and dentinogenic ghost cell tumor are generally not found in the pediatric age group, hence, are outside the scope of this book.

MESENCHYME AND/OR ODONTOGENIC ECTOMESENCHYME WITH OR WITHOUT INCLUDED ODONTOGENIC EPITHELIUM

- Odontogenic fibromas (epithelium poor and epithelium rich)
- Odontogenic myxoma/fibromyxoma
- Cementoblastoma.

ODONTOGENIC FIBROMA

The odontogenic fibroma is an elusive and controversial tumor, elusive because of its rarity and controversial because of the uncertainty as to the number of distinct types that exist.

Two types

1. Central
2. Peripheral.

Central odontogenic fibroma

The central odontogenic fibroma (COF), as the name implies, is a benign odontogenic neoplasm occurring within the jaws.

Pathogenesis

Based on its anatomic distribution and histological appearance, this neoplasm is considered to be a tumor of the mesenchymal components of the odontogenic apparatus—the periodontal ligament, dental papilla or dental follicle.

Clinical features

- Very uncommon tumor
- Occurs in the age range of 4 to 80 years
- Females are more commonly affected as compared to males
- Occurrence in maxilla is more common than in mandible
- Usually occurs as a painless swelling with slow, progressive growth, frequently resulting in cortical expansion
- Mobility of teeth may be seen.

Radiographic features

- Well-defined unilocular or multilocular radiolucent lesions often associated with teeth
- Root resorption is a common finding
- 12 percent of the cases have radiopaque flakes.

Histopathologic features

They show considerable diversity.

Types

They are of two types:

1. *Simple odontogenic fibroma*: Composed of stellate fibroblasts, often arranged in whorled pattern with fine collagen fibrils.
 - Small foci of odontogenic islands may or may not be present
 - Occasional foci of dystrophic calcification may be present.
2. *WHO type (Fig. 7.35)*:
 - More complex pattern
 - Fibrous connective tissue with collagen fibers in an interlacing pattern
 - Odontogenic epithelium in the form of strands or cords
 - Calcifications may be present.

Management

Enucleation and vigorous curettage is the treatment of choice.

Peripheral odontogenic fibroma

It is usually considered as the soft tissue counterpart of the central lesion.

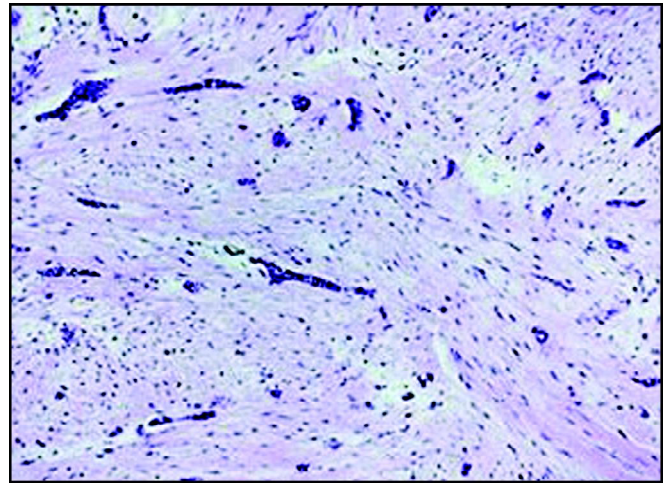


FIGURE 7.35: Histopathologic picture of central odontogenic fibroma showing thick collagen bundles with few inactive looking odontogenic islands

Clinical features (Fig. 7.36)

- Occurs in the age range of 5 to 65 years
- No gender predilection is seen
- Occurrence in mandible is more as compared to maxilla
- Presents as a slow growing, firm gingival mass.

Radiographic features

- Peripheral variant does not have any radiographic features
- May show saucerization of bone due to pressure effect.

Histopathologic features (Fig. 7.37)

- Mature, cellular fibrous connective tissue stroma is seen
- Strands of odontogenic epithelium surrounding a small amount of calcified material is present
- Calcified mass may resemble bone, dentin-like or cementum-like material.

Management

Surgical excision with vigorous curettage is the treatment of choice.

ODONTOGENIC MYXOMA

Thoma and Goldman, 1947, introduced myxomas of the jaws to the society for the first time.²⁴ In the 1992 WHO classification, the term myxoma is used along with odontogenic myxoma and myxofibroma as alternative terms.

Pathogenesis

- *Adekeye et al, 1984*, stated that this lesion represents a degenerative form of odontogenic fibroma²⁵



FIGURE 7.36: Peripheral odontogenic fibroma presenting as a swelling in the upper and lower anterior regions of the jaws

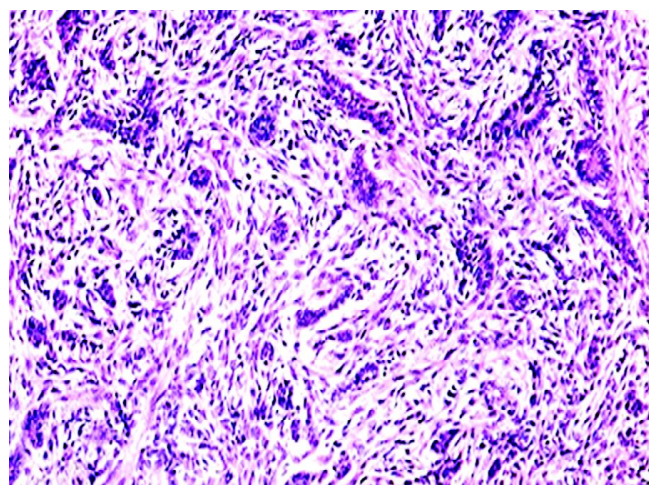


FIGURE 7.37: Histopathologic picture of peripheral odontogenic fibroma showing inactive looking odontogenic epithelium amongst scattered pleomorphic fibroblasts

- The classification of the odontogenic myxoma as an odontogenic tumor has been justified by its frequent occurrence in adolescence, its association with missing or unerupted teeth and the sporadic presence of odontogenic epithelium within the neoplastic, myxomatous tissue.

Clinical features

- Occurs mainly between the age ranges of 1 to 73 years.
- No sex predilection is seen.
- Occurrence in mandible is more common as compared to the maxilla.
- Smaller lesions are discovered during routine radiography.
- Larger lesions are associated with painless expansion of bone.

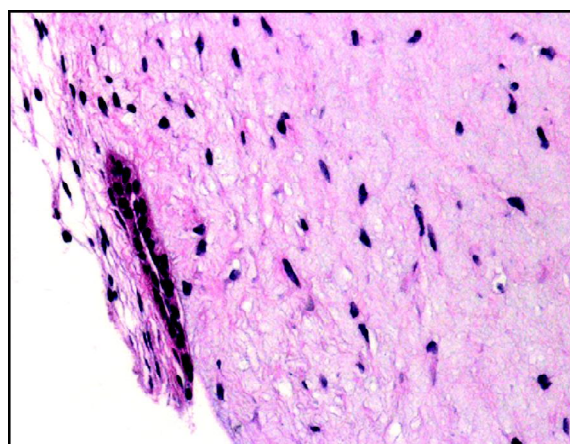


FIGURE 7.38: Histopathologic picture of odontogenic myxoma showing a hypocellular tumor with prominent myxoid stroma

Radiographic features

- Unilocular or multilocular radiolucency causing root resorption.
- Margins of the radiolucency are scalloped.
- Large myxomas may show soap bubble pattern.

Histopathologic features (Fig. 7.38)

- Haphazardly arranged stellate, spindle shaped and round cells in an abundant loose myxoid stroma that contains few collagen fibers.
- Small islands of odontogenic epithelium may or may not be present.

Management

1. Small lesions may be treated by curettage.
2. Larger lesions require extensive resection.

Note: Cementoblastoma is generally not seen in the pediatric age group, hence is not within the scope of this book.

MALIGNANT

ODONTOGENIC CARCINOMAS

- Metastasizing malignant ameloblastoma
- Ameloblastic carcinoma
 - Primary
 - Secondary (dedifferentiated), intraosseous
 - Secondary (dedifferentiated), extraosseous.
- Primary Intraosseous Squamous Cell Carcinoma (PIOSCC)
 - PIOSCC solid type
 - PIOSCC derived from odontogenic cysts

- PIOSCC derived from keratinizing cystic odontogenic tumor.

- Clear cell odontogenic carcinoma
- Ghost cell odontogenic carcinoma

ODONTOGENIC SARCOMAS

- Ameloblastic fibrosarcoma
- Ameloblastic fibrodentinosa sarcoma

METASTASIZING AMELOBLASTOMA

Emura, 1923, first reported the metastasis of solid/multicystic ameloblastoma to local lymph nodes.²⁶ **Vorzimer and Perla, 1932**, were the first to report metastasis of ameloblastoma to the right lung.²⁷

Pathogenesis

- Controversial in nature
- Authors predict that metastasis may be a result of multiple recurrences or either by implantation of the tumor into lymphatics and blood vessels.

Clinical features

- Occurs in the age range of 5 to 74 years
- Males are more commonly affected as compared to females
- Occurrence in mandible is more common as compared to maxilla
- Swelling, pain, delayed tooth eruption, ulcerations were the signs and symptoms reported by **Reichart et al, 1995**²⁸
- Lung is the most common site for the tumor to metastasize.

Radiographic features

- Malignant ameloblastomas cannot be distinguished radiographically from their non-metastasizing counterparts
- Computed tomography (CT) and Magnetic resonance imaging (MRI) are required for diagnostic purposes.

Histopathologic features

- Neoplasm is characterized by irregular islands of odontogenic epithelium within the ectomesenchyme
- These components lack the features of malignancy.

Management

1. Radical resection with primary reconstruction is recommended.
2. Chemotherapy and radiotherapy as a palliative treatment along with aggressive surgical intervention.

AMELOBLASTIC CARCINOMA

Ameloblastic carcinoma is a subtype of primary intraosseous carcinomas exhibiting the features of both ameloblastoma and carcinoma. It is a rarely reported disorder in children and adults.

Corio et al, 1987, classified this tumor as any ameloblastoma in which there is histologic evidence of malignancy in the primary or recurrent tumor, regardless of whether it has metastasized or not.²⁹

Recently, a case report of an extremely rare occurrence of ameloblastic carcinoma located in the maxilla of a pediatric patient was presented by **Nalan Yazici et al** in 2006.³⁰

Types

- Central variant
- Peripheral variant.

Pathogenesis

Both the variants may arise either from their respective benign counterparts or may arise de novo.

Clinical features

- Swelling, pain, paresthesia are the common presenting features
- Rapid growth is a characteristic feature
- Dysphonia may be present.

Radiographic features

- Ill-defined radiolucencies are seen
- Foci of radiopacities due to dystrophic calcification may also be seen within the radiolucent lesion.

Histopathologic features (Fig. 7.39)

- Irregular islands and cords of odontogenic epithelium within the ectomesenchyme
- Nuclear hyperchromatism, increased nuclear cytoplasmic ratio, abnormal mitotic activity may be seen
- Stellate reticulum cells show less orderly pattern
- Few areas show clear cells.

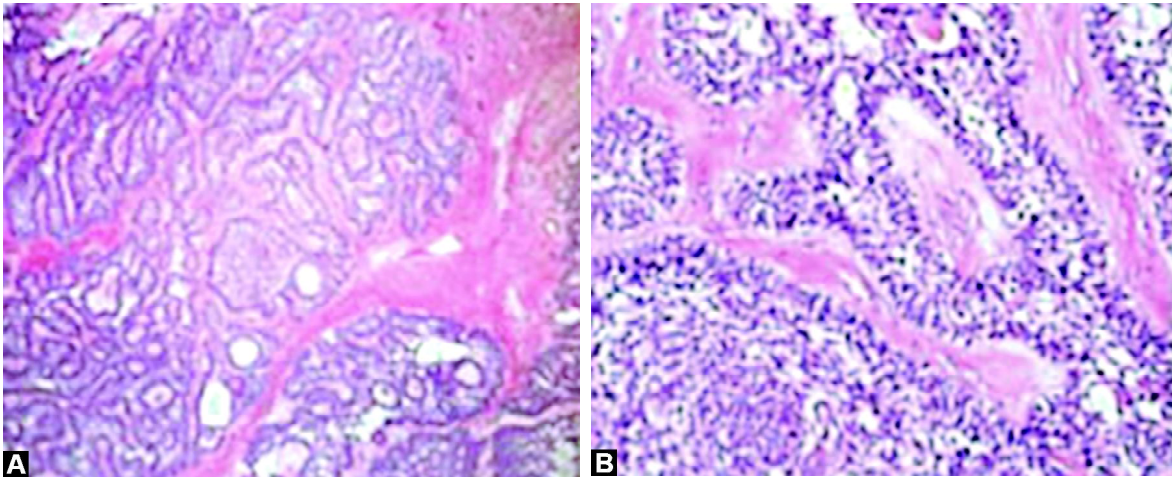
Management

Radical surgery with neck dissection is the treatment of choice.

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA (PIOSCC) SOLID TYPE

Morrison and Deeley stated that **Loos** in the year 1913, first described central squamous cell carcinoma of the jaw.³¹

Pindborg, 1971, suggested the term primary intraosseous squamous cell carcinoma.³²



FIGURES 7.39A and B: Histopathologic picture of ameloblastic carcinoma showing irregular islands and cords of dysplastic odontogenic epithelium within the ectomesenchyme

Pathogenesis

May originate from:

- Odontogenic epithelial cells consisting of reduced enamel epithelium
- Rests of Malassez in periodontal ligament
- Remnants of dental lamina in gingival tissue.

Clinical features

- Occurs in the age range of 4 to 81 years
- Males are more commonly affected as compared to females
- Occurrence in posterior mandible is more common as compared to maxilla
- Pain and swelling are common presenting signs
- Sensory disturbances may be present.

Radiographic features

Irregular diffuse radiolucencies are seen.

Histopathologic features

- Irregular odontogenic islands with basal type of cells showing palisading
- Squamous metaplasia and keratinization may be seen
- Since histopathological diagnosis is difficult, examination of serial sections is advised.

Management

Radical surgery with neck dissection is the treatment of choice.

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA (PIOSCC) DERIVED FROM ODONTOGENIC CYSTS

Primary intraosseous squamous cell carcinomas (PIOSCCs) are uncommon jaw malignancies derived from odontogenic epithelial remnants. The World Health Organization's classification of primary intraosseous carcinomas distinguishes among solid-type carcinomas, carcinomas originating from keratocystic odontogenic tumors (odontogenic keratocyst), and carcinomas derived from odontogenic cysts other than keratocystic odontogenic tumors. Most PIOSCCs associated with cysts are well-differentiated squamous cell carcinomas arising from residual periapical cysts and dentigerous cysts; PIOSCCs originating from odontogenic keratocysts and orthokeratinized odontogenic cysts are less common.

Pathogenesis

- Pathogenesis is unknown
- Long standing chronic inflammatory changes may be possible predisposing factors of malignant transformation of the epithelial lining of the cyst
- Keratinization of cyst epithelium may be associated with higher risk of malignant transformation.

Clinical features

- Occurs in the age range of 4 to 90 years
- Females are more commonly affected as compared to males
- Occurrence in mandible is more as compared to maxilla
- Recently, in 2008, an unusual case of a tumor resembling a primary intraosseous carcinoma arising from an

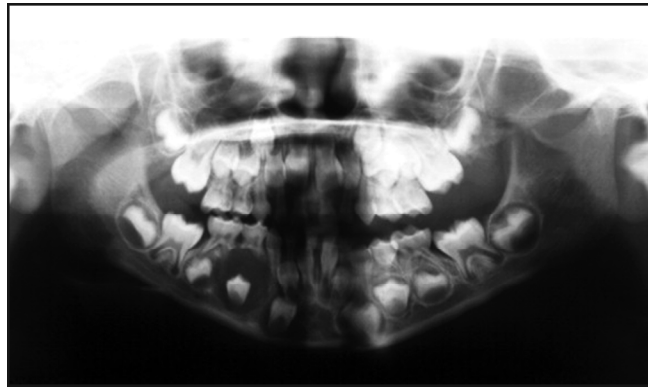
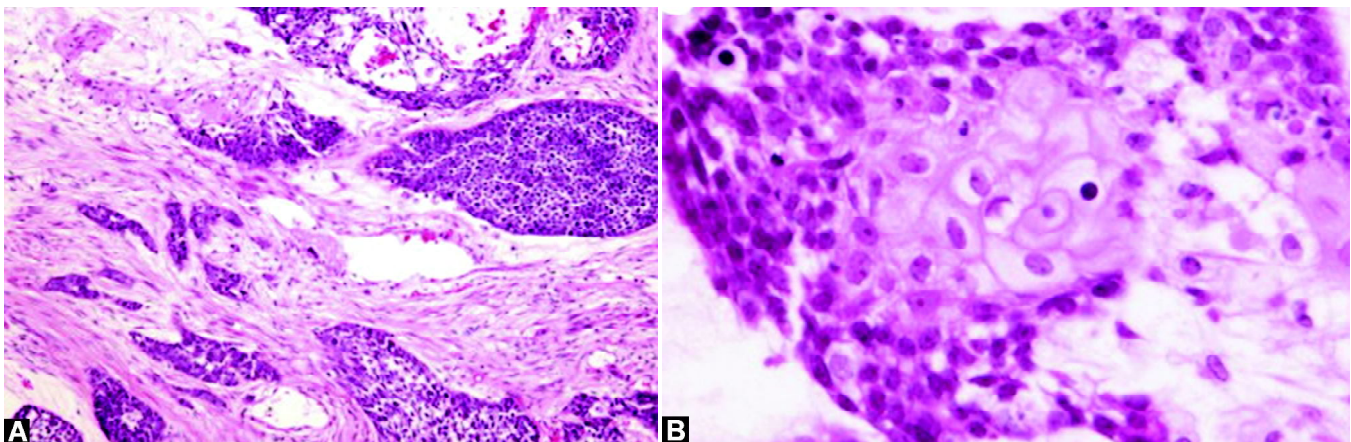


FIGURE 7.40: Radiographic picture of primary intraosseous squamous cell carcinoma (PIOSCC) derived from odontogenic cysts showing a lesion involving the developing tooth bud of the mandibular right first premolar with expansion of the contents of the crypt. Advanced root resorption of both the first and second deciduous molars is evident



FIGURES 7.41A and B: Histopathologic picture of primary intraosseous squamous cell carcinoma (PIOSCC) derived from odontogenic cysts showing islands and infiltrative cords of carcinoma cells with cohesive round cells and early squamoid differentiation

odontogenic cyst in a 5-year-old girl, with 7 years of follow-up after treatment was reported by *Makepeace Charles et al.*³³

Radiographic features (Fig. 7.40)

Radiolucency surrounded by well-defined radiopaque border.

Histopathologic features (Fig. 7.41)

- Transition between normal cyst epithelium and squamous cell carcinoma is seen
- Epithelium may show nuclear hyperchromatism, increased nuclear cytoplasmic ratio and abnormal mitosis
- Thickened fibrous capsule of the cyst is seen as a result of chronic inflammation.

Management

1. Surgical enucleation is the line of treatment for smaller lesions.
2. Radical surgery with neck dissection is the treatment of choice for larger lesions.

PIOSCC derived from keratinizing cystic odontogenic tumor, clear cell odontogenic carcinoma and ghost cell odontogenic carcinoma are generally not seen in the pediatric population and hence are outside the domain of this book.

AMELOBLASTIC FIBROSARCOMA

Heath, 1887, first described this lesion as a spindle cell sarcoma of the mandible.³⁴ The ameloblastic fibrosarcoma is a rare malignant neoplasm composed of benign odontogenic,

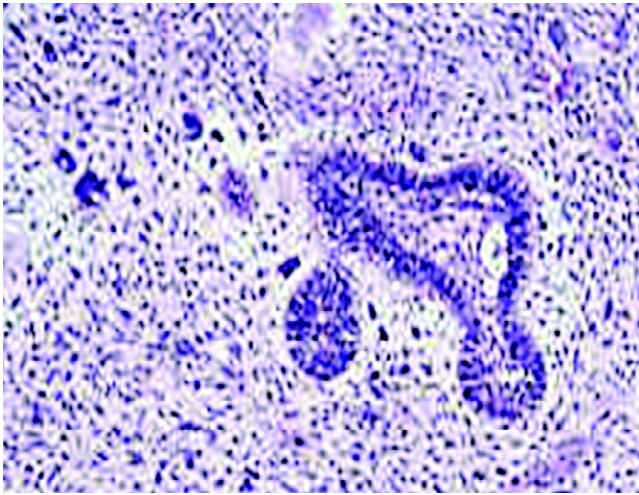


FIGURE 7.42: Histopathologic picture of ameloblastic fibrosarcoma showing islands of well-differentiated ameloblastic epithelium separated by a neoplastic stroma showing marked pleomorphism and mitotic activity

ameloblastomatous epithelium and malignant ectomesenchyme which resembles a fibrosarcoma. It is generally considered to be the malignant form of the ameloblastic fibroma in which the ectomesenchymal cells have retained their embryonic appearance and develop malignant characteristics.

Pathogenesis

Gradual transformation of ameloblastic fibroma to ameloblastic fibrosarcoma has been documented in a number of cases.

Clinical features

- Pain and swelling are the most constant findings
- Ulceration, bleeding, paresthesia of the lip have also been reported
- Mobility of teeth may also be seen
- Cervical lymphadenopathy and involvement of the submandibular lymph nodes is uncommon.

Radiographic features

- Irregular radiolucencies with indistinct margins are characteristic
- Large radiolucencies with a multilocular appearance and gross expansion and thinning of the cortical bone may be seen.

Histopathologic features (Fig. 7.42)

- Irregular islands and strands of odontogenic epithelium similar to that seen in solid/multicystic ameloblastoma

- Ectomesenchyme shows fibroblast-like cells that are pleomorphic, rounded or fusiform
- These cells display atypical and increased mitosis.

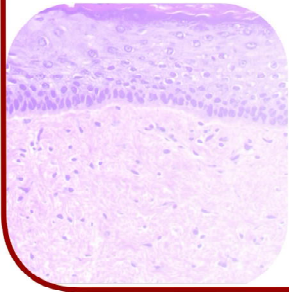
Management

Radical surgery with neck dissection is the treatment of choice.

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Epithelial Pathology in Children

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CHAPTER OVERVIEW

Introduction
Squamous papilloma
Verruca vulgaris (Common wart)
Condyloma acuminatum
Focal epithelial hyperplasia (Heck's disease)

Ephelis
Lentigo simplex
Pigmented nevi
Oral submucous fibrosis

INTRODUCTION

Epithelium is a tissue composed of cells that line the cavities and surfaces of structures throughout the body. There are four main types of tissues: epithelial, connective, muscular, and nervous. All of these tissues are found in our bodies, but epithelial tissue has a special function—it must cover all the surfaces of the body. Therefore, it is found in our skin, and it is also found covering all the surfaces of the openings (each one is called a lumen) within our bodies. The bottom edge of the epithelial tissue abuts the basement membrane; this bottom edge is called the basal surface. The edge of the epithelial tissue that faces the lumen (or the outside world) is called the apical surface. Cells within this tissue readily divide to make more cells. This helps this tissue recover after any sort of abrasions occur.

This tissue does not have any vasculature. The cells within this tissue are firmly attached to each other. Cell to cell junctions with each other are called tight junctions.

Functions of epithelial cells include secretion, selective absorption, protection, transcellular transport and detection of sensation. As a result, they commonly present extensive apical-basolateral polarity (e.g. different membrane proteins expressed) and specialization. Any structural or functional deviation from the normal may give rise to a variety of pathological entities of the epithelium termed as 'Epithelial Pathologies.' In this chapter, we shall discuss the epithelial pathologies commonly encountered in the pediatric population.



FIGURE 8.1: Squamous papilloma showing a pedunculated, painless, exophytic mass with papillary projections

SQUAMOUS PAPILLOMA (FIG. 8.1)

It is a benign neoplasm of epithelial tissue. It is thought to be induced by human papilloma virus (HPV) mainly the subtypes 6 and 11. The lesions are less virulent as compared to other lesions produced by HPV.

CLINICAL FEATURES

- No sex predilection
- **Greer and Goldman, 1974**, in their study on 110 cases reported that this lesion is most often seen in children, but may occur at any age¹

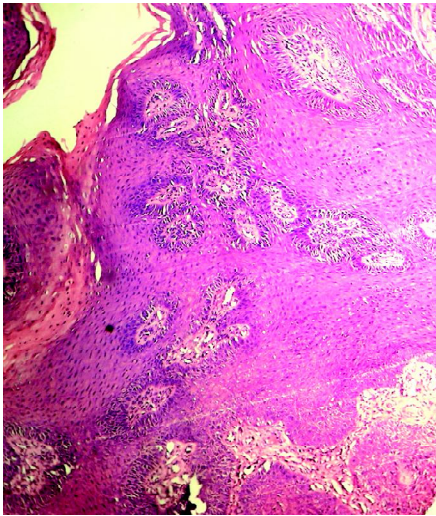


FIGURE 8.2: Histopathologic picture of squamous papilloma in which epithelium appears to be arranged in a papillary fashion

- Sites most commonly affected are tongue, lips and soft palate
- Occurs as a soft, pedunculated, painless, exophytic mass with papillary projections
- Due to the papillary projections, it is referred to as ‘*cauliflower-like*’
- It may appear normal, whitish or reddish in color depending on the amount of keratinization
- A rare form of disease termed as *laryngeal papillomatosis* is seen in both children and adults
- In children, hoarseness of voice may occur and blockage of the airways is the potential complication.

HISTOPATHOLOGIC FEATURES (FIG. 8.2)

- Proliferation of keratinized stratified squamous epithelium in the form of projections
- The underlying connective tissue is fibrocellular, with chronic inflammatory cell infiltrate
- Sometimes numerous virus altered cells termed *koilocytes* are seen in the spinous layer.

Management

1. Conservative surgical excision.
2. In case of laryngeal papillomatosis in children, radical surgical debulking is done as a treatment modality for relieving obstruction.

VERRUCA VULGARIS (COMMON WART)

It is a contagious disease causing focal hyperplasia of stratified squamous epithelium and is mostly associated with HPV subtypes 2, 4, 6 and 40.



FIGURE 8.3: Verruca vulgaris showing keratin horn on the index finger

CLINICAL FEATURES

- Mostly seen in children
- Pink, yellow or white, painless pedunculated or sessile papules with papillary projections mostly seen on the skin of hands
- Most common sites in the oral cavity are vermillion border of lip, labial mucosa and anterior tongue
- In some cases, cutaneous horn or keratin horns are seen on the skin surface that are produced as a result of continuous accumulation of keratin on the surface of skin that becomes hard (Fig. 8.3).

HISTOPATHOLOGIC FEATURES (FIG. 8.4)

- Epithelium is keratinized stratified squamous with acanthosis in the spinous cell layer
- Club shaped rete ridges are seen that are at the normal level as that of the normal adjacent tissue
- Sometimes numerous virus altered cells termed *koilocytes* are seen in the spinous layer
- Sometimes, epithelial cells show altered nucleus showing mitotic figures termed as *mitosoid cells*.

Management

The following modes of management may be employed:

1. Liquid nitrogen cryotherapy
2. Conservative surgical excision.
3. Curettage.
4. Topical application of keratinolytic agents mostly containing salicylic and lactic acid.
5. Use of lasers or electrosurgery.

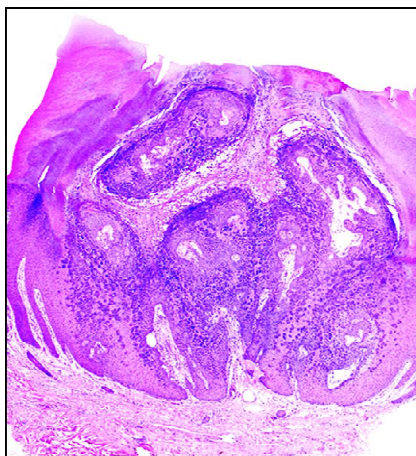


FIGURE 8.4: Histopathologic picture of verruca vulgaris showing keratinized stratified squamous epithelium with acanthosis in the spinous cell layer and club shaped rete ridges

CONDYLOMA ACUMINATUM (FIG. 8.5)

Condyloma acuminatum is one of the most common sexually transmitted diseases in the world. It is a venereal wart induced by human papilloma virus (HPV) of any of the following types 2, 6, 11, 53 and 54. In anogenital lesions, high risk type 16 and 18 are also found. It is usually considered to be a sexually transmitted disease. The incubation period of the virus averages two to three months.

CLINICAL FEATURES

- It occurs as a fleshy exophytic, sessile, well-demarcated, painless lesion of anogenital region
- It may be seen in the oral cavity due to autoinoculation or orogenital sexual practice. **Knapp and Uohara, 1967**, were the first to report such a case in the oral cavity²
- In the oral cavity, it occurs as a sessile, pink, well-demarcated lesion on labial mucosa, soft palate and lingual frenum
- It usually occurs in children and young adults, is uncommon in young children with a peak from 12 to 16 years
- In children, its occurrence may raise the issue of sexual abuse.

HISTOPATHOLOGIC FEATURES (FIG. 8.6)

- Lesional tissue is covered by stratified squamous epithelium with marked acanthosis
- Mild form of papillomatosis and hyperkeratosis may be seen
- Vacuolization of granular cells and pyknotic nuclei in prickle cell layer are observed. Such cells with pyknotic nuclei surrounded by clear zone are termed as **koilocytes**³
- Special immunochemical staining used is MIB-1 immunostaining in nuclei of upper two-thirds of epidermis



FIGURE 8.5: Condyloma acuminatum appears as a sessile, pink, well-demarcated lesion

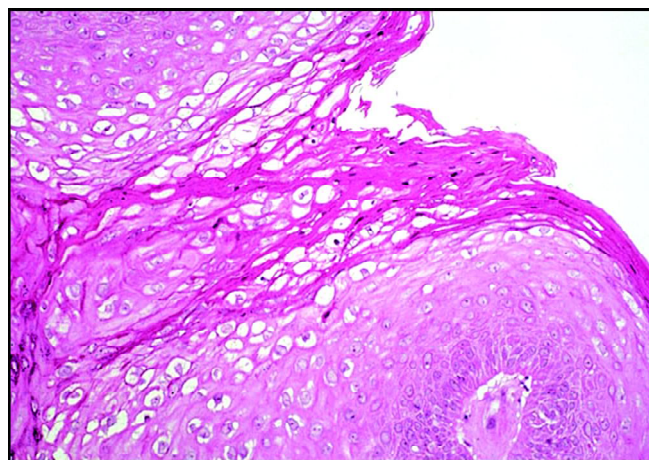


FIGURE 8.6: Histopathologic picture of condyloma acuminatum showing vacuolization of granular cells and pyknotic nuclei in prickle cell layer surrounded by clear zone termed as 'koilocytes'

that correlates with presence of HPV in lesions in which morphology is suggestive, but not diagnostic of condyloma.⁴

Management

1. Conservative surgical excision.
2. Laser ablation, but it carries the risk of airborne spread of HPV through aerosolized microdroplets.

FOCAL EPITHELIAL HYPERPLASIA (HECK'S DISEASE) (FIG. 8.7)

Focal epithelial hyperplasia is essentially an oral infection with the wart-producing papilloma virus type 13 and possibly type 32. It was first described in 1965 in Native Americans.⁵



FIGURE 8.7: Focal epithelial hyperplasia showing slightly elevated and well-demarcated plaques

CLINICAL FEATURES

- Heck's disease primarily occurs in children, but lesions may occur in young and middle-aged adults
- There is no gender predilection
- Sites of greatest involvement include the labial, buccal and lingual mucosa, but gingival and tonsillar lesions have also been reported
- Individual lesions are broad-based or slightly elevated so as to present as well-demarcated plaques
- They may frequently appear papillary in nature, but relatively smooth-surfaced, flat-topped lesions are more commonly seen
- Papules and plaques are usually the color of normal mucosa, but may be pale or, rarely, white
- Hyperplastic lesions are small (0.3–1.0 cm), discrete and well-demarcated, but they frequently cluster so closely together that the entire mucosal area takes on a cobblestone or fissured appearance.

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows stratified squamous epithelium showing hyperplasia, sometimes with considerable focal acanthosis.
- The thickened mucosa extends upwards, not down into underlying connective tissues, hence, the lesional rete ridges are at the same depth as the adjacent normal rete ridges.
- The ridges themselves are widened, often confluent and sometimes club-shaped. Some superficial keratinocytes show a koilocytic change similar to that seen in other HPV infections; while occasional others demonstrate a collapsed nucleus which resembles a mitotic figure (mitosoid cell). These presumably result from viral alteration of the cells.



FIGURE 8.8: Ephelis showing multiple, light tan colored macules

- Virus-like particles have been noted ultrastructurally within both cytoplasm and nuclei of cells within the spinous layer, and this layer is positive for HPV antigen with *in situ* hybridization.

Management

Conservative surgical excision is the treatment of choice.

EPHELIS (FIG. 8.8)

Ephelides are sun-induced freckles which are most common in fair-skinned individuals especially those with red or auburn hair.

CLINICAL FEATURES

- Ephelis usually appear as hyperpigmented macules and represent a region of increased melanin production
- They are more common in children and are less frequent with increasing age
- They occur as autosomal dominant trait
- No sex predilection
- They are usually uniform, multiple, light tan in color and less than 3 mm with regularly defined borders. They are transient and related to sun exposure
- They often appear on vermillion border of lips, with greater frequency on lower lip. Because ephelides require sun exposure they do not occur intraorally.

HISTOPATHOLOGIC FEATURES (FIG. 8.9)

Histologically there is increased pigmentation of basal cell layer without increase in melanocytes or elongation of rete pegs. The epidermis is normal.

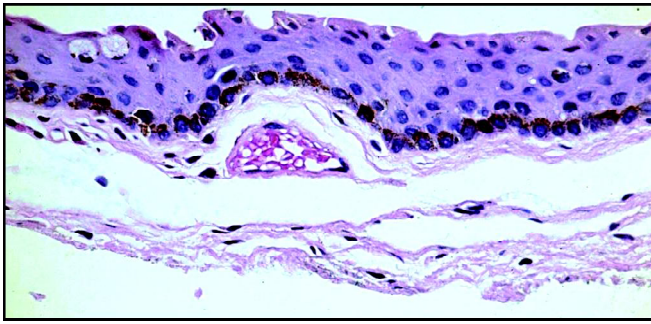


FIGURE 8.9: Histopathologic picture of ephelis showing increased pigmentation of basal cell layer



FIGURE 8.10: Lentigo simplex showing brown to black round macules

Management

1. No specific treatment.
2. Use of sunscreens can prevent darkening of existing lesions.

LENTIGO SIMPLEX (FIG. 8.10)

A lentigo [lentigines (*plural*)], is a small, sharply circumscribed, pigmented macule surrounded by normal-appearing skin. Lentigines may evolve slowly over years, or they may be eruptive and appear rather suddenly. Pigmentation may be homogeneous or variegated, with a color ranging from brown to black. They are thought to represent the early stages of melanocytic nevus.

CLINICAL FEATURES

- Lentigo simplex (also called simple lentigo, juvenile lentigo) is the most common form of lentigo
- Lentigo simplex is not induced by sun exposure and it is not associated with systemic disease

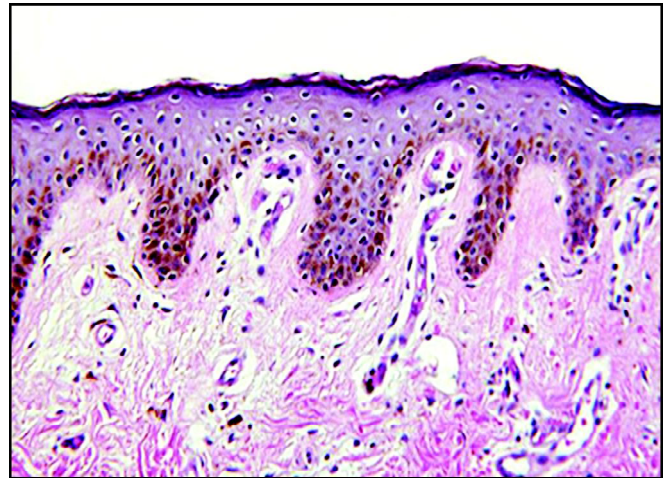


FIGURE 8.11: Histopathologic picture of lentigo simplex showing hyperplasia of the epidermis and increased pigmentation of the basal layer with variable number of melanocytes

- Clinically, the lesions are round or oval asymptomatic macules that are 3 to 15 mm in diameter
- Their margins can be either jagged or smooth
- Pigmentation is evenly distributed, with a color ranging from brown to black
- The lesions are few in number and may occur anywhere on the skin or mucous membranes
- The lesions usually appear first in early childhood, but they can also be present at birth or develop later.

HISTOPATHOLOGIC FEATURES (FIG. 8.11)

- Histopathologic findings may include hyperplasia of the epidermis and increased pigmentation of the basal layer
- A variable number of melanocytes are present; these melanocytes may be increased in number, but they do not form nests.

Management

1. No specific treatment.
2. Conservative surgical excision for esthetic purpose.

PIGMENTED NEVI

Nevus is a general term that may refer to any congenital lesion of various cell types or tissue types such as epidermis, vessels and pigmented cells.⁶

Nevus here refers to the pigmented lesion composed of nevus cells. These cells lack a dendritic process but otherwise are similar to melanocytes. They have the same enzyme, tyrosinase and this enzyme is responsible for conversion of tyrosine to melanin in the melanosome organelle.



FIGURE 8.12: Pigmented nevus seen on the palate as a round bluish-black area

These cells are found in the epithelium and connective tissue but the origin is not clear. It has been postulated that they are derived from pigment cells that migrate from neural crest to the epithelium and submucosa, or that may develop from altered resident melanocytes.

The lesion they cause is not a true neoplasm but represents a developmental malformation.

CLINICAL FEATURES (FIG. 8.12)

- Pigmented nevi are rarely seen in the oral mucosa and if present are located on the lower lip and less commonly on the tongue, gingiva, hard palate and buccal mucosa.
- They may appear at birth, puberty or in early adulthood and are more common in females.
- They are raised, well-demarcated discrete lesions varying from light brown to blue-black lesions and they do not blanch on pressure.
- In the oral cavity, the intramucosal nevus is more common and is seen in 55 percent of the cases, followed by blue nevi seen in 36 percent of the cases.
- The pigmented nevi are of 4 types:
 1. Junctional
 2. Compound
 3. Intramucosal and
 4. Blue nevi.
- The blue nevus occurs as a single, smooth, firm, round or oval bluish-black or blue area less than 1 cm in size and is commonly seen on the palate.
- *Andres Pinto et al, 2003*, reported the first documented case of epitheloid blue cell nevus involving the oral mucosa.⁷
- The cellular blue nevus is a less common lesion but often clinically similar to the common blue nevus. These lesions tend to be large, usually measuring 1 to 3 cm in diameter.

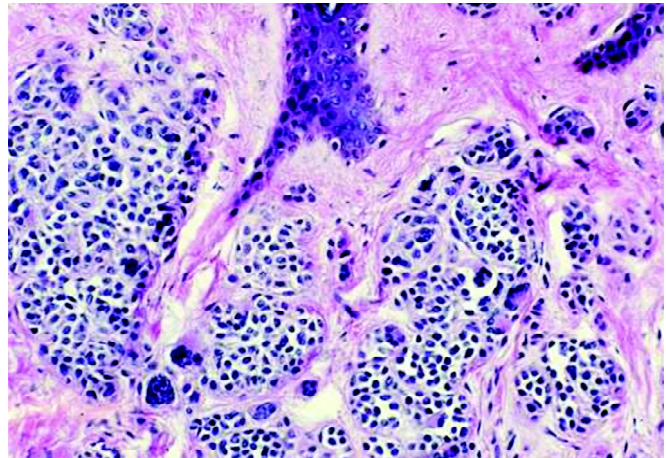


FIGURE 8.13: Histopathologic picture of pigmented nevus showing fibroblast-like spindle cells with fasciculation

Lesions are elevated, smooth-surfaced papules or plaques that are gray-blue to bluish black in color. Lesions are usually solitary and found on the buttocks, the sacral region and occasionally on the dorsal aspects of the hands and the feet.

- Blue color of the nevi is explained by **Tyndall effect**. This relates to the interaction of light with particles in a colloidal suspension.
- In case of blue nevus, melanin particles are deep to the surface, so that the light reflected back has to pass through the overlying tissue. Color with long wavelength (red and yellow) tends to be more readily absorbed by the tissues; shorter wavelength blue light is more likely to be reflected back to the observer's eye.
- Compound nevus is a lesion composed of two elements: an intradermal nevus and overlying junctional nevus.
- White, non-pigmented nevi of the oral mucosa have also been reported and these non-pigmented nevi appear as raised pink to white plaques.
- These pigmented nevi have a potential for malignant transformation. An increase in size, inflammation or increase in intensity of color of pigmented nevi specially Junctional and Compound type are **danger** signs and require immediate attention. Blue nevus may also undergo malignant transformation but the prognosis is better.

HISTOPATHOLOGIC FEATURES (FIG. 8.13)

- The essential component of the Junctional, Compound and Intramucosal type is the nevus cell, the location of which helps in distinction of the three types.⁸
- The nevus cell is a small, round or polyhedral cell with a distinctly outlined homogeneous or clear cytoplasm and a centrally located nucleus. The cells are usually found in clusters or groups and they contain melanin.

- In junctional nevus, the nevus cells are limited to the lower layers of the epithelium at the connective tissue junction and there are long epithelial ridges.
- In intramucosal nevus, the epithelium is normal and nevus cells are seen only in the connective tissue.
- In compound nevus, the nevus cells are seen both in the lower layers of epithelium and connective tissue.
- The blue nevus is composed of fusiform cells or fibroblast-like spindle cells with fasciculation that contain melanin and these cells are in masses. Sometimes they resemble Schwann-cells. A cellular variant of blue nevus called cellular blue nevus is composed of large plump melanoblasts and can be mistaken for melanoma. However this is a benign lesion but can metastasize into the lymph nodes.
- In common blue nevus, a vaguely nodular collection of poorly melanized spindle melanocytes and deeply pigmented dendritic melanocytes within thickened collagen bundles are seen. Scattered melanophages are usually noted. No mitoses are present.
- In cellular blue nevus, a well-demarcated nodule formed by fascicles and nests of tightly packed, moderately sized, spindle to oval melanocytes with scattered melanophages is seen.
- The lesion is centered in the reticular dermis; blunt-ended, bulbous extensions that extend into the subcutaneous fat may be noted. Occasional mitoses may be present, but significant cytologic atypia and areas of necrosis are absent. Often, a component of common blue nevus is seen within these lesions.
- A number of variants of blue nevi with corresponding histologic changes have been described, including epithelioid blue nevus, atypical blue nevus, deep penetrating blue nevus, sclerosing blue nevus and amelanotic blue nevus.
- The term malignant blue nevus is synonymous with malignant melanoma arising in association with a cellular blue nevus or growing in a histologic pattern similar to that of a cellular blue nevus.
- These lesions typically have a pronounced cytologic atypia, hyperchromasia, necrosis, an increased mitotic rate, and an infiltrative growth pattern.

Management

1. No medicinal therapy is available.
2. Biopsy should be performed on any pigmented lesion that changes with time.
3. For a solitary lesion, simple excision is usually curative.

ORAL SUBMUCOUS FIBROSIS (FIG. 8.14)

In 1952, Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease he discovered



FIGURE 8.14: Oral submucous fibrosis showing thick fibrous bands on the buccal mucosa in a 14-year-old boy

in five Indian women from Kenya.⁹ Joshi subsequently coined the term oral submucous fibrosis (OSF) for the condition in 1953.¹⁰ The condition was reported first by Paymaster for its precancerous potential. It is particularly associated with areca nut chewing, the main component of betel quid.¹¹

Betel quid is a combination of the areca nut (fruit of the *Areca catechu* palm tree, erroneously termed betel nut) and betel leaf (from the *Piper betel*, a pepper shrub), tobacco, slaked lime (calcium hydroxide) and catechu (extract of the *Acacia catechu* tree). Lime acts to keep the active ingredient in its freebase or alkaline form, enabling it to enter the bloodstream via sublingual absorption.

ETIOPATHOGENESIS

- The pathogenesis of the disease is not well-established, but the cause of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chillies, genetic and immunologic processes, nutritional deficiencies and other factors.
- Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150 percent.¹²
- Keratinocyte growth factor-1, insulin like growth factor-1, and interleukin 6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up-regulated in persons with oral submucous fibrosis due to areca quid chewing and arecoline may be responsible for their enhanced expression.¹³⁻¹⁵
- Further studies have shown that arecoline is an inhibitor of metalloproteinases (particularly metalloproteinase-2) and a stimulator of tissue inhibitor of metalloproteinases,

thus decreasing the overall breakdown of tissue collagen.¹⁶ Flavanoid, catechin and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation.¹⁷

- This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. Oral submucous fibrosis remains active even after cessation of the chewing habit, suggesting that components of the areca nut initiate oral submucous fibrosis and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen.
- Areca nuts have also been shown to have a high copper content and chewing areca nuts for 5 to 30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in persons with oral submucous fibrosis by stimulating fibrogenesis through up-regulation of copper-dependent lysyl oxidase activity.¹⁸
- The role of chilli ingestion in the pathogenesis of oral submucous fibrosis is controversial. A hypersensitivity reaction to chillies is believed to contribute to oral submucous fibrosis.
- A genetic component is assumed to be involved in oral submucous fibrosis. Patients with oral submucous fibrosis have been found to have an increased frequency of HLA-A10, HLA-B7 and HLA-DR3.¹⁹
- Some authors have demonstrated increased levels of proinflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with oral submucous fibrosis, which may be central to the pathogenesis of oral submucous fibrosis.²⁰
- Iron deficiency anemia, vitamin B complex deficiency and malnutrition are promoting factors that derange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring. The resulting atrophic oral mucosa is more susceptible to the effects of chillies and betel nuts.
- Some authors have found a high frequency of mutations in the APC gene and low expression of the wild-type TP53 tumor suppressor gene product in patients with oral submucous fibrosis, providing some explanation for the increased risk of oral squamous cell carcinoma development in patients with oral submucous fibrosis.²¹ Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis.²²

CLASSIFICATION

- There are several classification systems based on different aspects of OSF, e.g. classification systems based on clinical features given by Pindborg JJ in 1989, Lai DR in 1995, Ranganathan K et al in 2001 and Rajendran R in 2003; classification systems based on histopathological features

given by Pindborg et al in 1966 and Utsunomiya H et al in 2005; classification systems based on clinical and histopathological features by Khanna JN et al in 1995.

- Khanna JN and Andrade NN, 1995, developed a group of classification system for the surgical management of OSF.²³

Group I: Very Early Cases

- Common symptom is burning sensation in the mouth
- Acute ulceration and recurrent stomatitis
- Not associated with mouth opening limitation.

Histopathologic features

- Fine fibrillar collagen network interspersed with marked edema
- Blood vessels dilated and congested
- Large aggregate of plump, young fibroblasts present with abundant cytoplasm
- Inflammatory cells mainly consists of polymorphonuclear leukocytes with few eosinophils
- Epithelium normal.

Group II: Early Cases

- Buccal mucosa appears mottled and marble-like
- Widespread sheets of fibrosis palpable
- Patients with an interincisal distance of 26 to 35 mm.

Histopathologic features

- Juxtaepithelial hyalinization present
- Collagen present as thickened but separate bundles
- Blood vessels dilated and congested
- Young fibroblasts seen in moderate number
- Inflammatory cells mainly consists of polymorphonuclear leukocytes with few eosinophils and occasional plasma cells
- Flattening or shortening of epithelial rete pegs evident with varying degree of keratinization.

Group III: Moderately Advanced Cases

- Trismus evident, with an interincisal distance of 15 to 25 mm
- Buccal mucosa appears pale and firmly attached to underlying tissues
- Atrophy of vermillion border
- Vertical fibrous bands palpable at soft palate, pterygo-mandibular raphe and anterior faucial pillars.

Histopathologic features

- Juxtaepithelial hyalinization present
- Thickened collagen bundles faintly discernible, separated by very slight residual edema
- Blood vessels, mostly constricted
- Mature fibroblasts with scanty cytoplasm and spindle-shaped nuclei

- Inflammatory exudates consists mainly of lymphocytes and plasma cells
- Epithelium markedly atrophic with loss of rete pegs
- Muscle fibers seen interspersed with thickened and dense collagen fibers.

Group IVA: Advanced Cases

- Trismus is severe with interincisal distance of less than 15 mm
- The fauces is thickened, shortened and firm to palpation
- Uvula is shrunk and appears as small, fibrous bud
- Tongue movements limited
- On palpation of lips, circular band felt around entire mouth.

Group IVB: Advanced Cases with Premalignant and Malignant Changes

Hyperkeratosis, leukoplakia, or squamous cell carcinoma can be seen.

Histopathologic features

- Collagen hyalinized as smooth sheet
- Extensive fibrosis obliterated the mucosal blood vessels and eliminated the melanocytes
- Fibroblasts were markedly absent within the hyalinized zones
- Total loss of epithelial rete pegs
- Mild to moderate atypia present
- Extensive degeneration of muscle fibers evident.

CLINICAL FEATURES

- Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues).
- It mostly occurs in adults and very few cases have been seen in children.²⁴
- The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx.
- Progressive inability to open the mouth (trismus) due to oral fibrosis and scarring.
- Oral pain and a burning sensation upon consumption of spicy foodstuffs.
- Increased salivation.
- Change of gustatory sensation.
- Hearing loss due to stenosis of the eustachian tubes.
- Dryness of the mouth.
- Nasal tonality to the voice.
- Dysphagia to solids (if the esophagus is involved).
- Impaired mouth movements (e.g. eating, whistling, blowing, sucking).

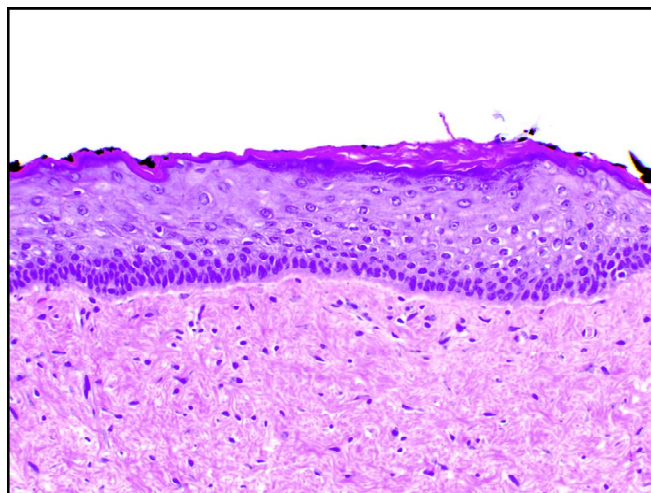


FIGURE 8.15: Oral submucous fibrosis showing diffuse hyalinization of subepithelial stroma with few, small fibroblastic nuclei and with pigment incontinence from the overlying epithelial melanin

HISTOPATHOLOGIC FEATURES (FIG. 8.15)

- Epithelium in early lesions shows sub-epithelial vesicles whereas hyperkeratosis with atrophy is seen in advanced cases
- Connective tissue shows dense collagen fibers, sometimes compressing the blood vessels that lead to deprivation of nutrition to the epithelium causing epithelial atrophy
- Chronic inflammatory cell infiltrate is evident in the connective tissue
- Epithelial dysplasia is found in 10 to 15 percent of all cases.

Management

The treatment of patients with oral submucous fibrosis depends on the degree of clinical involvement.

Treatment strategies include the following:

1. Steroids: In patients with moderate oral submucous fibrosis, weekly submucosal intralesional injections or topical application of steroids may help prevent further damage.
2. Placental extracts: The rationale for using placental extract in patients with oral submucous fibrosis derives from its proposed anti-inflammatory effect, hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human placental extract (Placentrex) has shown marked improvement of the condition.²⁵
3. Hyaluronidase: The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of

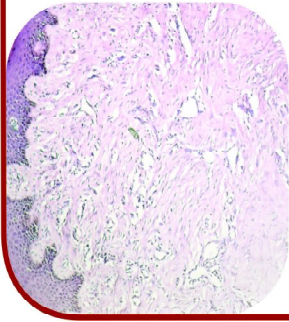
steroids and topical hyaluronidase shows better long-term results than either agent used alone.²⁶

4. IFN-gamma: This plays a role in the treatment of patients with oral submucous fibrosis because of its immunoregulatory effect. IFN-gamma is a known antifibrotic cytokine. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor in the treatment of patients with oral submucous fibrosis and intralesional injections of the cytokine may have a significant therapeutic effect on oral submucous fibrosis.²⁷
5. Lycopene: Newer studies highlight the benefit of this oral nutritional supplement at a daily dose of 16 mg. Mouth opening in 2 treatment arms (40 patients total) was statistically improved in patients with oral submucous fibrosis. This effect was slightly enhanced with the injection of intralesional betamethasone (two 1-ml ampules of 4 mg each) twice weekly, but the onset of effect was slightly delayed.²⁸
6. Pentoxifylline: In a pilot study, 14 test subjects with advanced oral submucous fibrosis given pentoxifylline at 400 mg 3 times daily were compared to 15 age- and sex-matched diseased control subjects. Statistical improvement was noted in all measures of objective (mouth opening, tongue protrusion, and relief from fibrotic bands) and subjective (intolerance to spices, burning sensation of mouth, tinnitus, difficulty in swallowing, and difficulty in speech) symptoms over a 7-month period.²⁹ Further studies are needed, but this could be used in conjunction with other therapies.
7. The role of these treatments is still evolving. The US Food and Drug Administration has not yet approved these drugs for the treatment of oral submucous fibrosis.
8. Surgical treatment is indicated in patients with severe trismus and/or biopsy results revealing dysplastic or neoplastic changes. Surgical modalities that have been used include the following:
 - a. Simple excision of the fibrous bands: Excision can result in contracture of the tissue and exacerbation of the condition.
 - b. Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Trismus associated with oral submucous fibrosis may be due to changes in the temporalis tendon secondary to oral submucous fibrosis; therefore, skin grafts may relieve symptoms.
 - c. Nasolabial flaps and lingual pedicle flaps: Surgery to create flaps is performed only in patients with oral submucous fibrosis in whom the tongue is not involved.
 - d. Use of a KTP-532 laser release procedure was found to increase mouth opening range in 9 patients over a 12-month follow-up period in one study.³⁰

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Connective Tissue Pathology in Children

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CHAPTER OVERVIEW

Introduction
Myofibroma
Pyogenic granuloma
Peripheral ossifying fibroma
Melanotic neuroectodermal tumor of infancy
Congenital epulis of newborn
Hemangiomas
Nasopharyngeal angiofibroma

Lymphangioma
Rhabdomyoma
Fibrosarcoma
Osteosarcoma
Rhabdomyosarcoma
Synovial sarcoma
Alveolar soft part sarcoma

INTRODUCTION

Connective tissue is a tissue that fills the interstices between more specialized elements and serves to hold them together and support them. It develops from mesenchyme, an embryonic type of tissue. It anchors, binds and supports various cells, tissues and organs in the body. The matrix of connective tissue consists of fibers, ground substance and tissue fluid. Any form of mutation in the components of connective tissue either genetic or environmental or due to some other conditions leads to connective tissue pathologies. This chapter focuses on the connective tissue pathologies that are seen in children.

MYOFIBROMA

Myofibromas are mesenchymal tumors that are commonly found in the dermis or subcutaneous tissue and are rarely found in muscle or bone. They were first described by **Stout** in 1954¹ and further classified by **Chung and Enzinger** in 1981.²

There are three types of infantile myofibromas: solitary myofibroma, multicentric fibromatosis without visceral involvement, and multicentric fibromatosis with visceral involvement. The prognosis is good for patients with a solitary myofibroma or multicentric myofibromatosis without visceral involvement because these lesions often regress spontaneously. Conversely, myofibromatosis with visceral involvement can be

fatal within days or weeks of birth, usually as a result of pulmonary or gastrointestinal involvement.³

CLINICAL FEATURES

- Incidence of occurrence in first four decades with mean age of 27 years.
- Solitary nodules and diffuse myofibromatosis usually occur in the head and neck.
- Most commonly affects males.
- Superficial tumors usually present as palpable, rubbery, firm nodules that are freely mobile, while deeper lesions are typically fixed.
- In the oral cavity, most commonly seen on lips, cheek and tongue.

RADIOGRAPHIC FEATURES

Well defined and multilocular radiolucent appearance.

HISTOPATHOLOGIC FEATURES

- They are characterized by presence of myofibroblastic spindle cells arranged in bundles or fascicles, often with areas of extensive hyalinization (Fig. 9.1).
- Tumor cells are positive for smooth muscle actin and muscle specific actin.

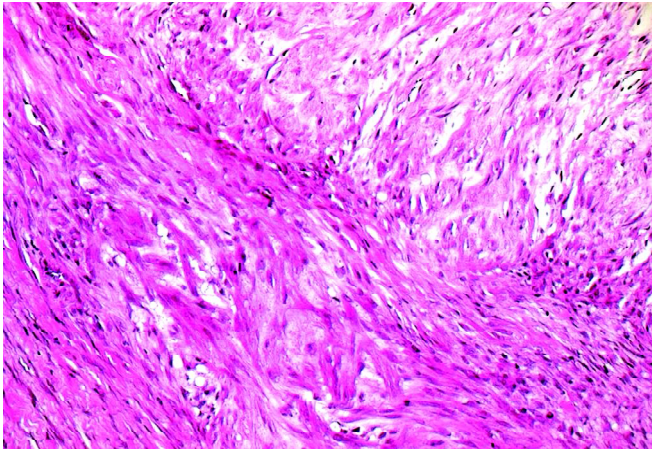


FIGURE 9.1: Histopathologic picture of myofibroma showing spindle cells arranged in fascicles

Management

1. Surgical excision.
2. In cases where surgery might cause major morbidity, chemotherapy is an option for reducing the size of the lesion and alleviating associated symptoms.⁴

PYOGENIC GRANULOMA

Pyogenic granulomas are benign vascular lesions that occur most commonly on the acral skin and also on oral mucous membranes of children. The term pyogenic granuloma is a misnomer. It is now referred to as telangiectic granuloma. Originally, these lesions were thought to be caused by bacterial infection; however, the etiology has not been determined. They are thought to be reactive in nature caused by exuberant tissue response to local irritation or trauma.

CLINICAL FEATURES

- Incidence of occurrence in children and young adults with male predilection in children and female predilection in young adults.
- Usually occurs as a pedunculated or sessile, smooth and lobulated mass (Fig. 9.2).
- Surface is characteristically ulcerated and color ranges from pink to red to purple.
- Young lesions appear reddish due to high vascularity as compared to older lesions that appear more pink due to presence of collagenized tissue.
- Bleeds easily due to extreme vascularity.
- In the oral cavity, it occurs most commonly on the gingiva, where gingival inflammation and irritation resulting from poor oral hygiene act as precipitating factors.
- Other common sites in the oral cavity are lip, tongue and buccal mucosa.

- Occurs more commonly on maxillary gingiva as compared to mandibular gingiva.
- Anterior areas of jaws are more commonly affected as compared to posterior areas.

RADIOGRAPHIC FEATURES

- Usually resorption of the underlying bone is evident. This may be due to the pressure phenomenon caused by the lesion on adjacent bone.

HISTOPATHOLOGIC FEATURES (FIG. 9.3)

- Lesional tissue shows highly vascular proliferative areas resembling granulation tissue with numerous small and large endothelium lined vascular channels engorged with red blood cells.



FIGURE 9.2: Pyogenic granuloma showing a sessile, lobulated mass

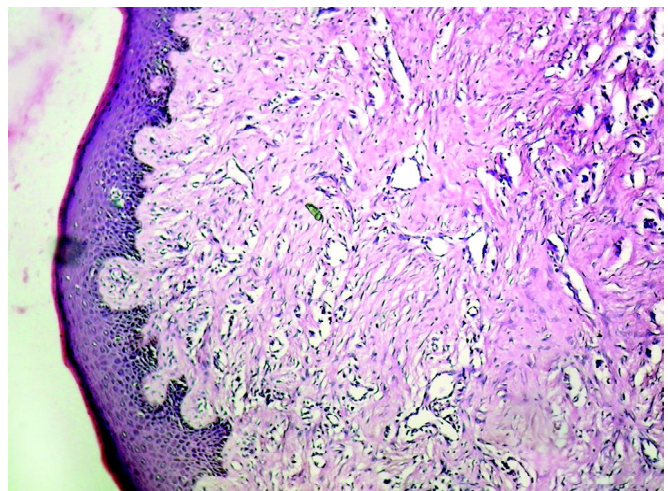


FIGURE 9.3: Histopathologic picture of pyogenic granuloma showing highly vascular proliferative areas resembling granulation tissue

- Chronic inflammatory cell infiltrate consisting of plasma cells and lymphocytes is evident. Neutrophils if present are mostly seen near the ulcerated surface.
- Older lesions appear more fibrous. Thus it is suggested that gingival fibromas of the oral cavity represent pyogenic granulomas that have undergone fibrous maturation.

Management

1. Conservative surgical excision. The excision should extend down to periosteum and adjacent teeth.
2. Thorough scaling should be done to remove any source of irritation and to prevent recurrence.
3. Therapy with the pulsed-dye laser at vascular-specific 585 nm is very selective, usually requires no anesthesia and produces excellent cosmetic results. The pulsed-dye laser works quite well for intraoral pyogenic granulomas.
4. Cryotherapy or silver nitrate therapy may be effective for very small lesions; however, treatment failure rates are high.
5. In pediatric cases, a eutectic mixture of local anesthetics (EMLA) applied to the lesion and surrounding skin under an occlusive dressing for 1 to 2 hours prior to additional intralesional anesthesia may be of significant value.

PERIPHERAL OSSIFYING FIBROMA

Peripheral ossifying fibroma (POF) is a reactive, relatively common gingival growth. *Shepherd* first reported this entity as alveolar exostosis in 1844.⁵ The main etiological factors of POF are trauma and chronic irritation, particularly from subgingival plaque and calculus.⁶ Moreover, the occurrence of this lesion

associated with an orthodontic appliance was detected in 3.8 percent of cases described by *Buchner and Hansen*⁷ and seven percent of pediatric cases described by *Cuisia and Brannon*.⁸ Inflammatory hyperplasia originating in the superficial periodontal ligament is considered to be a factor in the histogenesis of peripheral ossifying fibroma.⁹

CLINICAL FEATURES (FIG. 9.4)

- Peripheral ossifying fibroma presents as a painless, hemorrhagic and often lobulated mass of gingiva or alveolar mucosa
- A lesion may vary somewhat in size over time, depending on the amount of superficial inflammation and edema.
- Color of the lesion ranges from red to pink with ulcerated or non-ulcerated surface.
- They may often be mistaken for pyogenic granuloma.
- Mostly occurs in teenagers and young adults.
- Females are more commonly affected than males.
- Most common site of occurrence is maxillary anterior region of the jaw.
- Rarely migration or loosening of teeth is visible due to the pressure phenomenon of the lesion on the underlying bone.

RADIOGRAPHIC FEATURES

Radiographs may show irregular, scattered radiopacities in the lesion.

HISTOPATHOLOGIC FEATURES (FIG. 9.5)

- An aggregated submucosal proliferation of primitive oval and bipolar mesenchymal cells is the hallmark of peripheral ossifying fibroma.



FIGURE 9.4: Peripheral ossifying fibroma presenting as a painless lobulated mass

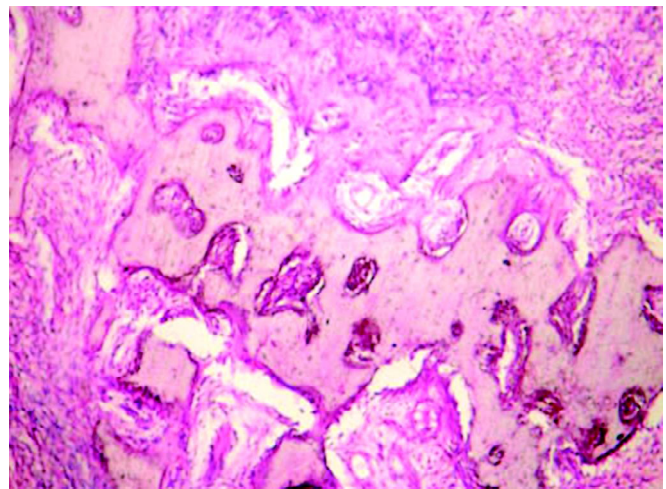


FIGURE 9.5: Histopathologic picture of peripheral ossifying fibroma showing islands and trabeculae of woven or lamellar bone surrounded by cellular stroma

- The lesion may be very cellular or may be somewhat fibrotic, but scattered throughout are islands and trabeculae of woven or lamellar bone, usually with abundant osteoblastic rimming. Metaplastic bone may also be seen.
- The calcified tissues may have the dark-staining, acellular, rounded appearance of cementum, in which case the term peripheral cementifying fibroma has traditionally been used. Many examples show an admixture of bone and cementum, i.e. peripheral ossifying/cementifying fibroma, and early lesions may contain only small ovoid areas of dystrophic calcification.
- Few cases show presence of multinucleated giant cells.

Management

1. Local surgical excision.
2. The excision should extend down to periosteum and adjacent teeth.
3. Thorough scaling should be done to remove any source of irritation and to prevent recurrence.

MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY (FIG. 9.6)

Melanotic neuroectodermal tumor of infancy (MNTI) is a relatively uncommon tumor of infancy that primarily affects jaws of newborn infants. It was initially reported by Krompecker in 1918 as congenital melanocarcinoma.¹⁰

In 1966, **Borello and Gorlin** reported a case with high urinary excretion of vanillylmandelic acid (VMA), suggesting a neural crest origin, and they proposed the term melanotic neuroectodermal tumor of infancy.¹¹

Paulo Eduardo Alencer et al 1999, selected three cases of melanotic neuroectodermal tumor of infancy and stated that MDM-2 expression may be important for development of

melanotic neuroectodermal tumor of infancy and that melanocytic cell population is the proliferative component of tumor.¹²

CLINICAL FEATURES

- More than 90 percent cases present within the first year of life, usually from age one month to six months. Mean age of patients with MNTI is 4.3 months.
- Male to female ratio is 6:7. More than 90 percent of cases occur in the head and neck region with most occurring on the anterior part of maxillary ridge. Other common sites include skull, mandible, epididymis and brain.
- The lesion appears as a sessile or slightly pedunculated, lobulated, firm mass which typically has a deep blue or black surface discoloration.
- It is often rapidly growing, non-ulcerated and darkly pigmented.
- Lesion can destroy the developing deciduous and permanent dentition.

RADIOGRAPHIC FEATURES

It presents as an unilocular or rarely as a multilocular radiolucency.

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows non-encapsulated, infiltrating tumor mass of cells arranged in pattern of alveolus like spaces, lined by cuboidal or large polygonal cells.
- These cells have pale abundant cytoplasm and nuclei with finely dispersed chromatin which may contain melanin pigment (Fig. 9.7).



FIGURE 9.6: Melanotic neuroectodermal tumor of infancy showing a non-ulcerated, sessile, lobulated, firm mass

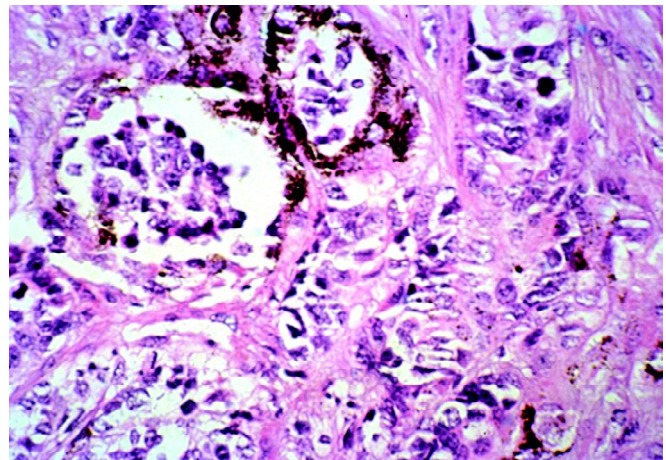


FIGURE 9.7: Histopathologic picture of melanotic neuroectodermal tumor of infancy showing cells arranged in pattern of alveolus like spaces and containing melanin

- Melanosomes are present in the cytoplasm and the cells are immunoreactive for cytokeratin and melanoma-associated antigen (HMB-45). Some lesional cells react for neuron specific enolase (NSE), synaptophysin and Leu-7 as well.

Management

1. Wide surgical excision of the lesion is performed. This treatment can usually be accomplished with a partial maxillectomy by using a Weber-Fergusson incision and a facial degloving approach. Teeth, developing teeth and the adjacent bone must be sacrificed when they lie near the borders of MNTI.
2. In instances of inoperable recurrence or where clear margins are impossible to obtain, radiation therapy and/or chemotherapy have been used, but too few examples exist for preferences to be established.

CONGENITAL EPULIS OF NEWBORN

The word **epulis** is derived from the Greek word, meaning “on the gum” or “gumboil” and has unfortunately been used for a variety of benign tumors and tumor-like conditions having dissimilar structures and histogenesis.¹³

Congenital epulis is a rare benign soft-tissue tumor that is also called “gingival granular cell tumor of the newborn” and was described first by **Neumann** in 1871.¹⁴ Although congenital epulis is composed of granular cells and is similar to the true granular cell tumor (granular cell myoblastoma), the histology and epidemiology of these two lesions differ. Granular cell tumors are less vascular and often have a component of pseudoepitheliomatous hyperplasia. They contain more conspicuous nerve bundles than do congenital epulides. Congenital epulides only occur in the gum pads of infants, whereas granular cell tumors usually occur in adults (between 20 and 60 years of age) and may involve multiple organs.¹⁵

The histogenesis of the lesion is uncertain, and proposed cells of origin include odontogenic epithelium, undifferentiated mesenchymal cells, pericytes, fibroblasts, smooth muscle cells, nerve related cells and histiocytes.^{16,17}

CLINICAL FEATURES

- Appears as smooth-surfaced, pedunculated and sometimes lobulated tumor arising from the alveolar crest of newborn infants (Fig. 9.8).
- The lesion is most common in females, with a female-to-male ratio of 8:1, and is three times more common in the maxilla than the mandible.¹⁸

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows a covering of stratified squamous epithelium.



FIGURE 9.8: Congenital epulis of newborn appearing as a smooth-surfaced, pedunculated and lobulated tumor

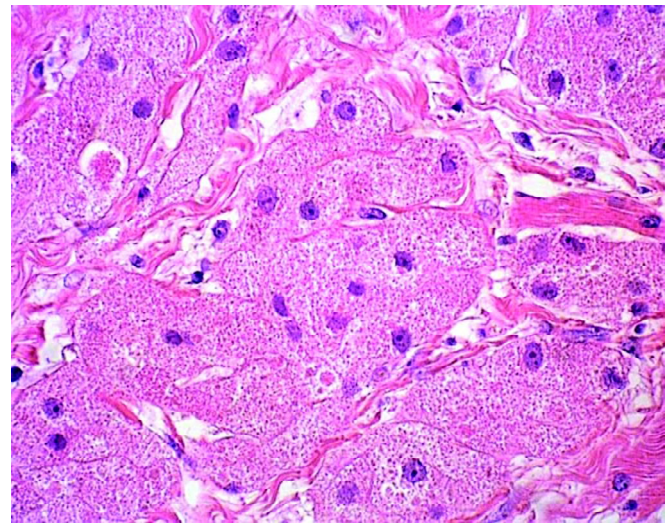


FIGURE 9.9: Histopathologic picture of congenital epulis of newborn showing large, rounded and polyhedral cells with eosinophilic granular cytoplasm and small, round or ovoid nuclei

- The cells appear large, rounded and polyhedral with eosinophilic granular cytoplasm and small, round or ovoid nuclei (Fig. 9.9).
- Blood vessels and collagen fiber bundles of various sizes are evident among the granular cell nests.
- Older lesions show elongated cells separated by fibrous connective tissue.
- Immunohistochemical examination reveals negativity of the granular cells for S-100 protein.

Management

Surgical excision of the lesion is the most preferred treatment.

HEMANGIOMA (FIG. 9.10)

The term hemangioma was originally used to describe any vascular tumour like structure, both present around birth or appearing later in life. In 1982, Mulliken and Glowacki separated these conditions into a family of self-involuting tumors (growing lesions that eventually disappear) from the family of malformations (enlarged or abnormal vessels present at birth and essentially permanent) (Table 9.1).¹⁹

A simple classification proposed by Watson and McCarthy based on 1,308 blood vessel tumors is as follows:²⁰

1. Capillary hemangioma
2. Cavernous hemangioma
3. Angioblastic or hypertrophic hemangioma
4. Racemose hemangioma
5. Diffuse systemic hemangioma

6. Metastasizing hemangioma
7. Nevus vinosus
8. Hereditary hemorrhagic telangiectasis.



FIGURE 9.10: Hemangioma appearing as a red colored, well-demarcated and flat lesion

TABLE 9.1: Classification of vasoformative tumors¹⁹

<i>Vasoformative tumor</i>	<i>New nomenclature</i>	<i>Old nomenclature</i>
Hemangiomas	Capillary hemangioma	Strawberry hemangioma
		Juvenile hemangioma
	Cavernous hemangioma	
	Mixed hemangioma	Parotid hemangioma
Vascular malformations	Venous malformation	Cavernous hemangioma
		Hemangiomatosis
	Intramuscular venous malformation	Intramuscular hemangioma
	Capillary malformation	Capillary hemangioma
		Port-wine stain
	Arteriovenous malformation	Arteriovenous hemangioma
		Arterial angioma
		Arteriovenous aneurysm
		Cirsoid angioma
		Red angioma
		Serpentine aneurysm
	Lymphatic malformation	Capillary lymphangioma
		Cavernous lymphangioma
		Lymphangioma
		Cystic hygroma

ETIOPATHOGENESIS

The cause of hemangioma is currently unknown; however, several studies have suggested the importance of estrogen signaling in hemangioma proliferation.

Vascular malformations need to be understood in terms of their embryology and development. The classic sequence of events usually falls into three stages:

1. The undifferentiated capillary network stage, in which the primitive mesenchyme is nourished by an interlacing system of blood spaces without distinguishable arterial and venous channels. The more common capillary hemangioma represents an arrest in the development of the mesenchyme primordia in the undifferentiated capillary network stage. As differentiation progresses, primitive vessels penetrate deeper into the subcutaneous layer, the muscle, or the bone tissue and give rise to capillary hemangiomas.
2. The retiform developmental stage, that begins at about 48 days of embryonic development and in which separate venous and arterial stems appear on either side of the capillary network. Termination of development in the retiform developmental stage may produce venous, arterial, or capillary malformations because this stage is characterized by an established venous, arterial and capillary system.
3. The final developmental stage that begins at two months' development and involves the gradual replacement of the immature plexiform network by the mature vascular channels. In the final developmental stage, the maturation of the venous and lymphatic systems predominates. Aberrations in this mature stage of development result in venous malformations and lymphangiomas.

Takahashi, 1994, hypothesized that during the third trimester of fetal development, immature endothelial cells coexist with immature pericytes, which maintain their proliferative capacity for a limited period during postnatal life.²¹ Angiogenic peptides, such as beta-fibroblast growth factor, vascular endothelial growth factor, and proliferating cell nuclear antigen, induce proliferation of these immature cells, resulting in the development of the hemangioma. As the endothelial cells differentiate, an influx of mast cells, various myeloid cells, and tissue inhibitors of metalloproteinases (TIMPs) occurs.²² TIMPs, along with interferon and transforming growth factor produced by the mast cells, terminate the endothelial cell proliferation and passively induce involution by senescence of endothelial cells.

In 2007, a paper from the Stanford Children's Surgical Laboratory revealed that localized soft tissue hypoxia coupled with increased circulating estrogen after birth may be the stimulus.²³ There is also a hypothesis presented by researchers at Harvard²⁴

and the University of Arkansas²⁵ that maternal placenta embolizes to the fetal dermis during gestation resulting in hemangio-magenesis; yet Duke researchers²⁶ conducted genetic analyses of small nucleotide polymorphisms in hemangioma tissue compared to the mother's DNA that contradicted this notion.

CLINICAL FEATURES

- Hemangiomas are approximately three to five times more common in females than in males.
- Mainly occur in infants and children. The incidence of hemangiomas increases to 23 percent in premature infants with a birthweight of less than 1000 g.
- It is a lesion of unknown etiology. One hypothesis postulates that placental cells, such as the trophoblast, may be the cell of origin for hemangiomas. Therefore, hemangiomas may arise secondary to some event *in utero*. However, conflicting evidence supports this hypothesis.
- Capillary hemangiomas are usually not present at birth but are antedated by a pale, well-demarcated, flat area, most visible with agitation. Gene map loci for capillary hemangiomas are 5q35.3, 5q31-q33, 4q12.
- Cavernous hemangiomas are composed of large, irregular, deep dermal and subcutaneous blood-filled channels that impart a purplish discoloration to the overlying skin. They are typically soft, poorly defined and readily blanch with compression.
- Mostly involved facial bones are mandible, maxilla and the nasal bones.
- Central jaw lesions can show hypermobility of the teeth and distortion of the arch form.
- Severe hemorrhage following dental extraction is not an uncommon presentation of central hemangiomas of the maxilla and the mandible.
- Common clinical findings in central hemangiomas of the jaws include gingival bleeding, postextraction bleeding, swelling, pain, mobility of the teeth and bony expansion.
- Root resorption of the teeth has been reported in 30 percent of cases, but the vitality of the teeth is usually not affected.
- Intramuscular hemangiomas in the oral region are most commonly seen in the masseter muscle.

RADIOGRAPHIC FEATURES

- Some of them show a "honeycomb" appearance on radiograph while sometimes it appears as a "sunburst" appearance as seen in osteosarcoma.
- Angiography is considered to be the most definitive for identification of a vascular lesion.
- Contrast enhanced MRI can be used to differentiate hemangioma from lymphangioma.

HISTOPATHOLOGIC FEATURES

- The usual hemangioma is composed of many small capillaries lined by a single layer of endothelial cells supported by connective tissue stroma of varying density (Fig. 9.11).
- Cavernous form of hemangioma consists of large dilated blood sinuses with thin walls each showing an endothelial lining. The sinusoidal spaces are usually filled with blood, although an admixture with occasional lymphatic vessels occurs in some instances (Fig. 9.12).
- Hemangiomas in their proliferative stages show endothelial cell hyperplasia forming syncytial masses, thickened endothelial basement membrane, and presence of large number of mast cells.

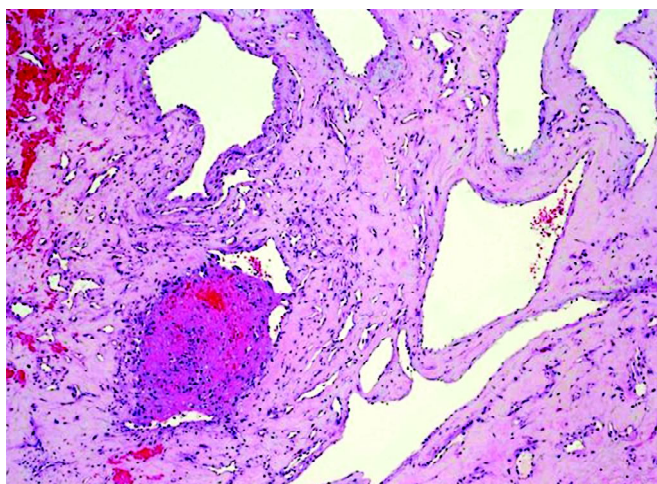


FIGURE 9.11: Histopathologic picture of capillary hemangioma showing numerous capillaries lined by a single layer of endothelial cells

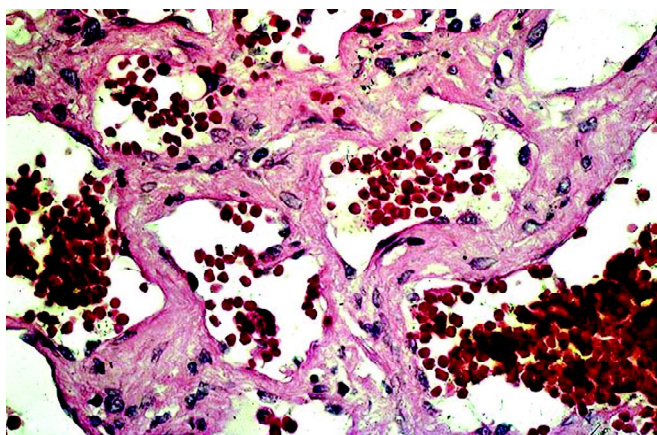


FIGURE 9.12: Histopathologic picture of cavernous hemangioma showing large dilated blood sinuses with thin walls each showing an endothelial lining

- Hemangiomas in their involuting phase show less mitotic activity, foci of fibrofatty infiltration and normal mast cell count.
- Hemangiomas are associated with the following syndromes:
 - **Rendu-Osler-Weber syndrome:** Autosomal dominant inheritance, multiple telangiectasis, occasional GI tract involvement, occasional CNS involvement.
 - **Sturge-Weber-Dimitri syndrome:** Noninherited and nonfamilial, portwine stain, leptomeningeal angiomas.
 - **Kasabach-Meritt syndrome:** Thrombocytopenic purpura associated with hemangioma, consumptive coagulopathy, microangiopathic hemolysis, intralesional fibrinolysis.

Management

1. Spontaneous regression occurs at an early age.
2. The two primary medical treatments are steroids and interferon therapy. Steroids have become a mainstay in the treatment of proliferating hemangiomas in infants and children. High doses of systemic or intralesional steroids are the first-line treatment and a dramatic response is observed in 30 percent of patients.²⁷
3. **Fost and Esterly** first reported the use of systemic steroids in the treatment of hemangiomas. Prednisone at a dose of 20 to 30 mg/d was given for two weeks to four months. Both of the patients with capillary hemangiomas had a definite response, and three of the four patients with mixed hemangiomas had a definite response. Fost proposed that therapy be discontinued if no response occurred after two weeks because of the multiple adverse effects of systemic steroids in infants.²⁸
4. **Pope et al** demonstrated in a randomized controlled trial that oral corticosteroids offered more clinical and biological benefit than pulse steroids, with a higher risk of adverse effects noted in 20 patients with problematic hemangiomas.²⁹
5. Frequent monitoring of blood pressure should be performed using the appropriately sized blood pressure cuff during the administration of systemic corticosteroid therapy.
6. **Greinwald et al** described a prospective randomized trial of interferon alfa-2a involving 24 patients with massive or life-threatening hemangiomas of the head and the neck. They were given daily subcutaneous injections for four months. Of those patients, 58 percent had a greater than 50 percent reduction in the size of the tumor and 42 percent had a complete response. Response rates were greater than those for corticosteroids (58% v/s 30%). Another investigation found that interferon alfa-2b was effective in reducing the size of the tumor in more than two-thirds of patients.³⁰

7. However, some concern exists regarding the toxicity of interferon alfa, especially in children. The most serious adverse effects include neurologic effects (e.g. spastic paresis, seizures, coma), hematologic effects (e.g. neutropenia, thrombocytopenia) and hepatic toxicity.
8. Complete surgical excision of these lesions offers the best chance of cure, but, often, because of the extent of these benign lesions, significant sacrifice of tissue is necessary.
9. Embolotherapy is one of the more commonly used adjunctive procedures in the treatment of vascular tumors. Embolization literally means the occlusion of a vessel by the introduction of a foreign body. In a broader definition, it also means any other occlusion that is obtained with a proliferating reaction of the vessel wall. In 1904, Dawbain, Lussenhop and Spence described the preoperative injection of melted paraffin-petrolatum into the external carotid arteries of patients with head and neck tumors. In 1930, Brooks introduced particulate embolization when he described the occlusion of a traumatic carotid-cavernous fistula by injecting a fragment of muscle attached to a silver clip into the internal carotid artery. Agents for embolotherapy can be broadly divided into two groups: absorbable materials and nonabsorbable materials (see the list below). The nonabsorbable materials can be further subdivided into particulate, liquid, sclerosing, and nonparticulate agents.

Embolotherapy agents:

- Absorbable materials
 - Autologous blood clot
 - Modified blood clot
 - Gelfoam
 - Oxycel
- Nonabsorbable materials
 - Particulate agents
 - i. Acrylic spheres
 - ii. Autologous fat of muscle
 - iii. Ferromagnetic microspheres
 - iv. Methylmethacrylate spheres
 - v. Polyvinyl alcohol (Ivalon)
 - vi. Silastic spheres
 - vii. Stainless steel pellets
 - Injectable (fluids)
 - i. Amino acid occlusion gel (Ethibloc)
 - ii. Isobutyl-2-cyanoacrylate
 - iii. Microfibrillar collagen (Avitene)
 - iv. Silicone rubber
 - Sclerosing agents
 - i. Absolute ethanol
 - ii. Boiling contrast medium
 - iii. Polidocanol
 - iv. Sodium morrhuate
 - v. Sodium tetradecyl sulfate (Sotradecol)

- Nonparticulate agents
 - i. Stainless steel coils
 - ii. Platinum coils
 - iii. Silk streamers
 - iv. Plastic brushes
 - v. Detachable balloons

10. In the treatment of vasoformative tumors, the resorbable materials are not particularly useful in the long term, except when they precede a surgical treatment and only short-term occlusion is required. Nonresorbable materials comprise the mainstay of embolotherapy for vasoformative tumors. Polyvinyl alcohol sponges (Ivalon) are obtained by reticulation of polyvinyl alcohol with formaldehyde. The sponge has the property of being compressible when wet and reexpanding to its original shape and size when a dried piece is placed in an aqueous solution, such as blood. These properties make Ivalon particularly well suited for large vessels, in which it produces a permanent occlusion.
11. Isobutyl-2-cyanoacrylate (IBCA) is a rapidly hardening plastic adhesive similar to superglue. The liquid plastic is readily injectable, even through very small catheters, and it polymerizes almost instantly upon contact with ionic fluids, such as blood or vascular endothelium. This polymerization leaves the plastic solid.
12. Absolute ethanol is used as a sclerosing agent. Its presumed mechanism of action is a direct toxic effect on the vascular endothelium that activates the coagulation system on the dehydrated endothelium. Thus, the vascular occlusion is not achieved instantly but rather in days to weeks. The toxic effect extends to the perivascular tissue, and the use of absolute ethanol has led to perivascular necrosis. Injection of alcohol into oral lesions is followed by marked swelling 6 to 8 hours later. By using small volumes and carefully avoiding direct deposition into the overlying mucosa, necrosis of the mucosa can usually be avoided. Other agents used for sclerosis of oral vascular tumors include sodium morrhuate, sodium tetradecyl sulfate (STS), and hydroxy-polyethoxydodecan (an agent that is a double hydrophilic and hydrophobic chain).
13. Use of laser therapy for the treatment of hemangiomas has gained popularity. Lasers have evolved to where more selective photothermolysis can be attained rather than nonselective tissue destruction.
14. The yellow light lasers (578 to 585 nm) are selectively absorbed by hemoglobin.
15. Oral mucosa may be amenable to these lasers because little melanin is present in the mucosa. Little to no damage to the mucosa or the epithelium has been reported. In the macular stage of development, a 585 nm pulsed dye laser has been used to treat a capillary hemangioma.³¹ The tunable dye laser

can ablate superficial ecstatic blood vessels without significant epidermal damage or scarring. However, the 585 nm pulsed dye laser has limited penetration (1 – 2 mm).

16. Apfelberg reported using a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser to treat massive hemangiomas and vascular malformations in the head and the neck via intralesional laser photocoagulation.³² The laser is theorized to institute an initial thrombogenesis in many areas of the hemangioma or the vascular malformation, and this event initiates involution by normal body processes. The Nd:YAG laser emits beams in the near infrared region of the spectrum (1064 nm). This laser has deep penetration (1 cm) and an excellent hemostatic capability that makes it more suitable for thicker, larger, more developed hemangiomas.
17. Cryosurgery for cutaneous lesions has been associated with scarring, but it may have a role in the treatment of oral mucosal lesions. Several authors have used cryosurgery for treating oral vascular tumors, although this technique has fallen into disfavor in recent years.
18. Surgery of intrabony lesions of the jaws is usually completed in combination with other procedures (e.g. embolization, sclerotherapy) to reduce blood loss.

NASOPHARYNGEAL ANGIOFIBROMA

Hippocrates described this tumor in the 5th century BC, but **Friedberg** first used the term angiofibroma in 1940. It is a rare, vascular and fibrous tumor-like lesion that occurs only in the nasopharynx.

ETIOPATHOGENESIS

- Although the etiology remains unknown, a hormonal theory has been suggested because of the lesion's occurrence in adolescent males.
- Other theories include a desmoplastic response of the nasopharyngeal periosteum or the embryonic fibrocartilage between the basiocciput and the basisphenoid.
- Etiology from nonchromaffin paraganglionic cells of the terminal branches of the maxillary artery has also been suggested. Comparative genomic hybridization analysis of these tumors revealed deletions of chromosome 17, including regions for the tumor suppressor gene *p53* as well as the *Her-2/neu* oncogene.

CLINICAL FEATURES

- Most commonly seen in males.
- Onset is most commonly in the second decade; the range is 7 to 19 years.

- Nasal obstruction is the most frequent symptom, especially in initial stages.
- Epistaxis is mostly unilateral and recurrent.
- Headache is seen especially if paranasal sinuses are blocked.
- Facial swelling may be evident.
- Other symptoms—Unilateral rhinorrhea, anosmia, hyposmia, rhinolalia, deafness, otalgia, swelling of the palate, proptosis, deformity of the cheek.
- Lesions in the oral cavity are rare.

RADIOGRAPHIC FEATURES

Characteristic features of anterior bowing of posterior wall of maxillary sinus may be evident on CT scan and MRI.

HISTOPATHOLOGIC FEATURES (FIG. 9.13)

Lesional area shows a dense fibrous connective tissue containing numerous dilated thin-walled blood vessels of variable size.

Management

1. The testosterone receptor blocker flutamide was reported to reduce stage I and II tumors to 44 percent.
2. Stereotactic radiotherapy (i.e. gamma knife) delivers a lower dose of radiation to surrounding tissues. However, most authorities reserve radiotherapy for intracranial disease or recurrent cases.
3. Three-dimensional conformal radiotherapy in extensive juvenile nasopharyngeal angiofibroma (JNA) or intracranial extension provides a good alternative to conventional radiotherapy regarding disease control and radiation morbidity.
4. A lateral rhinotomy, transpalatal, transmaxillary, or sphenoethmoidal route is used for small tumors.
5. The infratemporal fossa approach is used when the tumor has a large lateral extension. The midfacial degloving approach, with or without a LeFort osteotomy, improves posterior access to the tumor.
6. The facial translocation approach is combined with Weber-Ferguson incision and coronal extension for a frontotemporal craniotomy with midface osteotomies for access.
7. An extended anterior subcranial approach facilitates *en bloc* tumor removal, optic nerve decompression and exposure of the cavernous sinus.
8. Intranasal endoscopic surgery is reserved for tumors limited to the nasal cavity and paranasal sinuses. Some authors advocate its use for lesions with limited extension to the infratemporal fossa. Image-guided, endoscopic, laser-assisted removal has also recently been used.

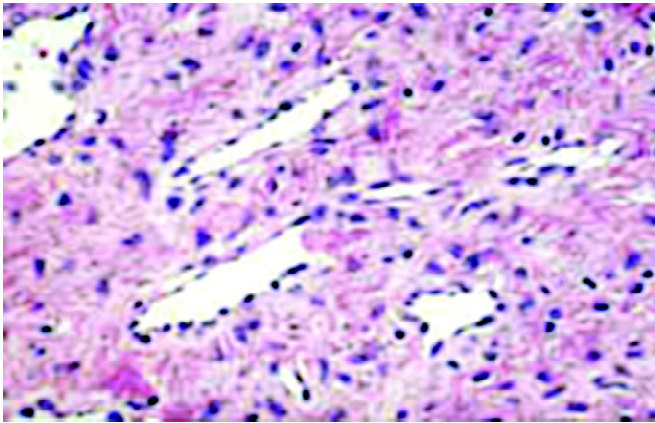


FIGURE 9.13: Histopathologic picture of nasopharyngeal angiofibroma showing numerous dilated blood vessels surrounded by connective tissue stroma

LYMPHANGIOMA

Lymphatic malformations were first described by **Redenbacher** in 1828. Many of the early researchers believed that lymphatic malformations were neoplasms. Currently, most researchers agree that lymphatic malformations are not neoplastic and have adopted the term “lymphatic malformation” to emphasize this fact.

ETIOPATHOGENESIS

Two major theories of development of the lymphatic system have been proposed to explain the origin of lymphatic malformations. **Sabin** proposed that the lymphatic system develops from five primitive sacs which sprout from the venous system. In the head and neck, endothelial outbuddings from the jugular sac spread centrifugally to form the lymphatic system.³³ **McClure and Huntington** proposed that the lymphatic system develops from mesenchymal clefts in the venous plexus reticulum and spread centripetally towards the jugular sac. Lymphatic malformations develop from sequestration or congenital blockage of the primitive lymphatic anlage.

A role of vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) had been shown in their studies by **Sidle et al.**³⁴

CLASSIFICATION

The most popular classification system was proposed by **Landing and Farber** in 1956. Lymphangioma simplex is composed of three walled lymphatic channels. Cavernous lymphangioma consists of dilated lymphatic spaces with increased fibrous tissue. They also tend to invade surrounding tissue. Cystic lymphangioma is made up of endothelial lined cysts varying in size from mm to several cm.³⁵

The different types of lymphangiomas are classified as follows:

- Lymphangioma circumscriptum is a simplex superficial red macular or vesicular lesion of mucous membranes or skin
- Lymphangioma capillary type is a simplex lesion of dilated capillary-like channels.
- Lymphangioma cavernosa is a simplex lesion of dilated lymphatic channels with deep extension and without cyst formation.
- Lymphangioma cystica (i.e. cystic hygroma) is composed of large lymphatic cysts that expand into adjacent soft tissue planes and are well defined, circumscribed or lobulated.
- Lymphangioma complex is composed of multiloculated poorly defined cysts extending to more than one anatomic area, tissue plane or organ system.

CLINICAL FEATURES

- Children or, less commonly, adults usually present with a mass in the head and neck area.
- Common head and neck sites in childhood are the cervical area, floor of the mouth and the tongue.
- Orofacial manifestations include mandibular or maxillary deformation, rotation, and malocclusion (i.e. crossbite).
- In a study by **Orvidas et al**, the most common location involved was the submandibular region, followed by the parotid and cheek.³⁶
- Most of the cases are reported at birth.
- Occur as soft, flaccid, fluctuant mass with a multilobulated consistency.
- Most common oral site is anterior two-third of the tongue, resulting in macroglossia.
- May be seen bilaterally on the mandibular ridge.

RADIOGRAPHIC FEATURES

- Radiographic findings are not so characteristic for this lesion.
- CT and MRI are most useful in determining proximity to vital structures and mediastinal involvement preoperatively.

HISTOPATHOLOGIC FEATURES

- Lesional tissue in case of cavernous lymphangioma is composed of lymphatic vessels that may show marked dilatation (Fig. 9.14)
- Cystic hygroma may show macroscopic cyst-like spaces. Spaces contain proteinaceous fluid and occasionally lymphocytes.
- Capillary lymphangioma contains numerous endothelium lined, blood filled channels.

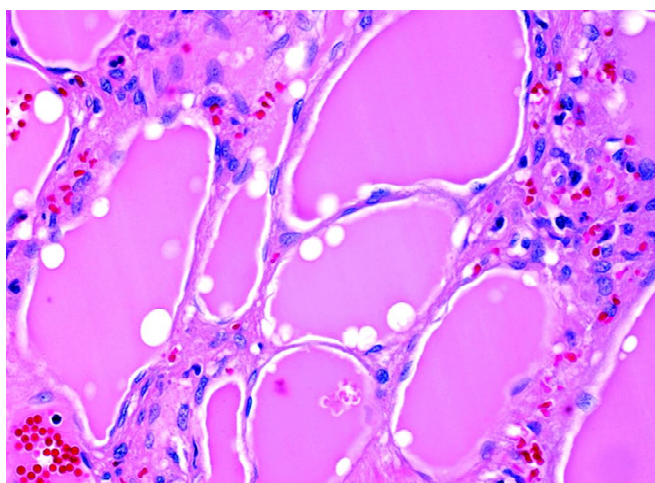


FIGURE 9.14: Histopathologic picture of cavernous lymphangioma showing lymphatic vessels containing fluid and lined by endothelial cells

Management

1. Surgical excision is the treatment of choice. The primary intention is to accomplish total resections.
2. Radiation therapy has been effective but abandoned because of later malignant transformation or retardation of growth sites.
3. Carbon dioxide laser therapy has been effective in managing upper airway lesions and superficial mucosal microcystic lesions.
4. Intralesional sclerotherapy with group A *Streptococcus pyogenes* of human origin (OK-432) has had some success controlling lymphangiomas. The mechanism suggested is the stimulation of increased permeability of the endothelium, accelerating lymphatic fluid drainage and size reduction of the lymphangioma.
5. Somnoplasty shows promise for reduction of tongue lymphatic malformations.
6. Occasional reports have described the use of triamcinolone, cyclophosphamide, bleomycin, fibrin glue, and alcohol (Ethibloc). Results have been inconsistent, and success is limited.

RHABDOMYOMA

Rhabdomyoma is an exceedingly rare tumor of striated muscle.

CLASSIFICATION

The two types of rhabdomyoma are neoplastic and hamartoma.

1. The neoplastic variety is subclassified into adult, fetal, and genital types.
2. Hamartomas are divided into cardiac rhabdomyoma and rhabdomyomatous mesenchymal hamartomas of the skin. Rhabdomyoma probably represents a genetic variant of

striated muscle development. Drugs or environmental factors have not been identified as causes of this neoplasm.

CLINICAL FEATURES

- Fetal rhabdomyoma occurs between birth and age three years.
- Lesions in fetal rhabdomyoma are usually found in the subcutaneous tissues of the head and neck (Fig. 9.15).
- Adult rhabdomyoma occurs in patients older than 40 years.
- Patients with adult rhabdomyoma might experience some hoarseness, difficulty in breathing, difficulty in swallowing or a combination. The lesions most commonly occur as round or polypoid mass in the region of the neck and mostly affect the oropharynx, the larynx, and the muscles of the neck.
- Genital rhabdomyoma is observed in young and middle-aged women.
- Patients with genital rhabdomyoma are young or middle-aged women presenting with vaginal masses.
- Cardiac rhabdomyomas occur chiefly, but not exclusively, in the pediatric age group.
- Patients with cardiac rhabdomyoma may present with a history of shortness of breath, heart murmurs and sometimes associated with signs and symptoms suggestive of cerebral palsy (suggesting the possibility of associated tuberous sclerosis).
- Rhabdomyomatous mesenchymal hamartoma of the skin is observed in newborns and infants.

HISTOPATHOLOGIC FEATURES

- Lesional tissue in **adult type** is composed of well-differentiated large cells that resemble striated muscle cells. Cross-striation has been demonstrated by phosphotungstic acid hematoxylin (PTAH), muscle specific actin, desmin, and myoglobin while dystrophin is shown to be expressed in the cell membranes. The cells are deeply eosinophilic



FIGURE 9.15: Rhabdomyoma presenting as a discrete nodular mass

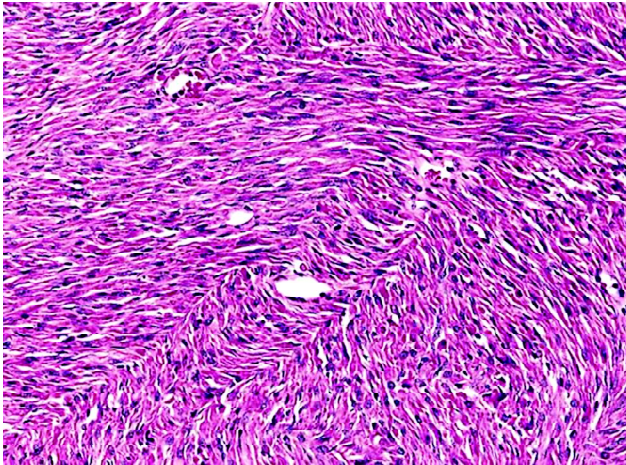


FIGURE 9.16: Histopathologic picture of fetal rhabdomyoma showing a mixture of spindle-shaped cells with indistinct cytoplasm and muscle fibers

polygonal cells with small peripherally placed nuclei and occasional intracellular vacuoles.

- Lesional tissue in **fetal type** is composed of a mixture of spindle-shaped cells with indistinct cytoplasm and muscle fibers, which resemble striated muscle tissue (Fig. 9.16).
- Lesional tissue in **genital rhabdomyoma** is composed of a mixture of fibroblast-like cells with clusters of mature cells containing distinct cross-striations and a matrix containing varying amounts of collagen and mucoid material.
- Lesional tissue in **rhabdomyomatous mesenchymal hamartoma** is composed of poorly oriented or perpendicular bundles of well-differentiated skeletal muscle with islands of fat, fibrous tissue and occasionally proliferating nerves.

Management

1. Proper medical assistance is required for these patients as they may experience difficulties in breathing and swallowing. In such instances, nasal oxygen may help patients with breathing difficulties. In circumstances in which swallowing is extremely difficult, supplemental intravenous fluids may be administered until surgery is performed.
2. Local surgical excision is the treatment of choice most of the time.
3. Fetal rhabdomyomas are usually located in the subcutaneous tissues. In most instances, they can be excised from various parts of the body without much difficulty.
4. Local excision is the treatment of choice for genital rhabdomyomas.
5. Open heart surgery may be necessary for the treatment of cardiac rhabdomyomas

FIBROSARCOMA

Fibrosarcomas are relatively uncommon tumors and account for 12 to 19 percent of soft tissue sarcomas. More than half of all tumors arise in the lower extremities; approximately 10 percent occur in the head and neck, most commonly in the sinonasal tract and neck.

ETIOLOGY

Fibrosarcomas arise from fibroblasts. The development of fibrosarcoma is associated with previous radiation therapy or burn injury; tumors are reported to arise in irradiated sites or burn scars. They are of two varieties, viz. adult and infantile.

CLINICAL FEATURES

- Fibrosarcomas may arise in patients of any age; a slight male predominance exists. Most cases occur in those aged 30 to 60 years.
- An infantile variant that occurs in patients younger than five years appears to represent a distinct subtype and is associated with a better prognosis. An association with trisomy of chromosomes 8, 11, 17 and 20 has been reported.
- They most commonly manifest as painless, gradually enlarging masses.
- They are homogeneous and nonenhancing on CT scan and they may cause bone remodeling.

HISTOPATHOLOGIC FEATURES

- Fibrosarcomas are divided into well-differentiated and poorly differentiated subtypes based on the degree of cellular uniformity, collagen production, and mitotic bodies.
- Well-differentiated or low-grade tumors have a uniform spindle-cell appearance, eosinophilic cytoplasm, tapered nuclei arranged in an interlocking fascicular or herring bone pattern and substantial collagen production (Fig. 9.17).
- Poorly differentiated or high-grade lesions have greater cellular variability, with hyperchromatism, an increased number of mitotic figures, scant collagen production and a greater degree of necrosis and hemorrhage. The infantile variant resembles the adult variant.

Management

Surgical excision including a wide margin of adjacent normal tissue.

OSTEOSARCOMA

Osteosarcoma is an ancient disease that is still incompletely understood. The term “sarcoma” was introduced by the English surgeon **John Abernathy** in 1804 and was derived from Greek words meaning “fleshy excrescence”. In 1805, the French

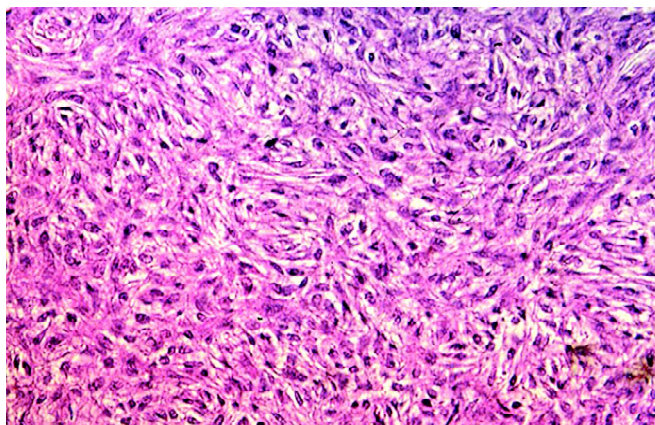


FIGURE 9.17: Histopathologic picture of well-differentiated fibrosarcoma showing uniform spindle-cell appearance, eosinophilic cytoplasm, tapered nuclei arranged in an interlocking fascicular or herring bone pattern

surgeon Alexis Boyer (personal surgeon to Napoleon) first used the term “osteosarcoma”. Boyer realized that osteosarcoma is a distinct entity from other bone lesions, such as osteochondromas (exostoses).^{37,38}

Osteosarcoma of jaws is uncommon and constitutes approximately 15 percent of all primary bone tumors confirmed at biopsy.³⁹ They affect most rapidly growing parts of the skeleton; metaphyseal growth plates in femur, tibia and humerus being the commonest sites. Etiology of the primary type is unknown; it may be due to genetic influence or other environmental factors. Secondary craniofacial osteogenic sarcomas occur in patients of skeletal Paget’s disease, fibrous dysplasia of bone and as a late sequela to craniofacial irradiation. Majority of craniofacial osteosarcomas occur in skeletally mature patients in contrast to those that affect the appendicular skeleton.

CLINICAL FEATURES

- Osteosarcoma of long bones presents as pain during activity as compared to osteosarcoma of jaw bones where swelling rather than pain is the commonest finding.
- In a study by **Forteza et al** on 81 cases of osteosarcoma, maxillary osteosarcomas occurred in females with the ratio of 4:1 whereas mandibular lesions occurred only in males.³⁹ Few reports state even distribution of the lesion between maxilla and mandible.
- May occur in both children and adults.
- A palpable mass may or may not be present. The mass may be tender and warm, although these signs are indistinguishable from osteomyelitis. Increased skin vascularity over the mass may be discernible. Pulsations or a bruit may be detectable.
- Decreased range of motion may be evident.
- Pathologic fractures may occur.

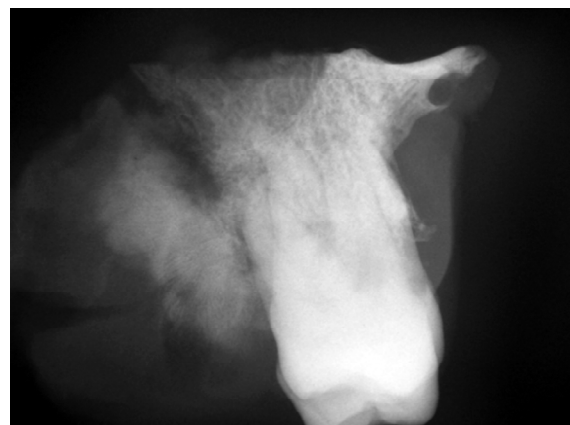


FIGURE 9.18: Radiographic picture of osteosarcoma showing ‘sun-ray appearance’

RADIOGRAPHIC FEATURES

- Osteosarcoma shows varied radiographic appearance ranging from osteolytic to mixed to osteogenic pattern of bone. If the tumor invades the periosteum, many thin irregular spicules of new bone may develop outwards and perpendicular to the surface of the lesion producing the so called ‘**sun ray appearance**’ (Fig. 9.18).

HISTOPATHOLOGIC FEATURES

- Depending upon the predominant type of extracellular matrix present, osteosarcomas are categorized histopathologically into osteoblastic, chondroblastic and fibroblastic subtypes.
- The osteoblastic variety consists of tumor osteoid surrounded by bizarrely arranged fibroblast-like cells.
- In chondroblastic osteosarcoma, tumor cells lie in the lacunae and form lobules. The center of lobule has bony trabeculae producing a feathery appearance, and towards the periphery, the tumor becomes hypercellular (Fig. 9.19).
- Fibroblastic osteosarcoma is the least common variant where the tumor cells are spindle shaped and characteristically arranged in herring bone pattern typically resembling fibrosarcoma. The formation of tumor osteoid differentiates this variant of osteosarcoma from fibrosarcoma.⁴⁰

Management

1. Wide radical resection is the treatment of choice for osteosarcoma of jaws. Surgery and adjuvant chemotherapy and radiotherapy may be required sometimes.
2. The presence of micro metastases decides the need of adjuvant therapy.

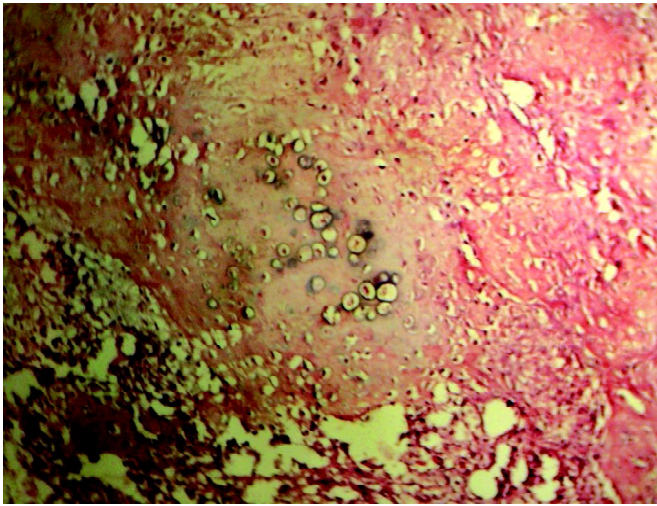


FIGURE 9.19: Histopathologic picture of chondroblastic osteosarcoma showing areas of atypical chondroid tissue seen with large chondrocytes surrounded by osteoid



FIGURE 9.20: Rhabdomyosarcoma presenting as a painless and infiltrative mass on left eye

RHABDOMYOSARCOMA (FIG. 9.20)

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. The name is derived from the Greek words *rhabdo*, which means rod shape, and *myo*, which means muscle. Although Weber first described rhabdomyosarcoma in 1854, a clear histologic definition was not available until 1946, when Stout recognized the distinct morphology of rhabdomyoblasts.⁴¹

The cause of rhabdomyosarcoma is unknown. Although it is hypothesized that alveolar variety occurs due to chromosomal translocations, namely, $t(2;13)$ or $t(1;13)$. The embryonal subtype usually has a loss of heterozygosity at band 11p15.5. This suggests a role of genetic alterations in formation of these tumors. They are basically of three varieties, viz. alveolar, embryonal and pleomorphic.

CLINICAL FEATURES

- Although the tumor is believed to arise from primitive muscle cells, tumors can occur anywhere in the body except bone. The most common sites are head and neck, extremities, genitourinary tract.
- Other notable sites include the trunk, orbit and retroperitoneum.
- Rhabdomyosarcoma occurs at other sites in less than three percent of patients. The botryoid variant of embryonal variety arises in mucosal cavities, such as the bladder, vagina, nasopharynx and middle ear.
- Lesions in the extremities are most likely to have an alveolar type of histology.
- The male-to-female ratio is 1.2 to 1.4:1.
- Most commonly seen in children, teenagers and young adults.
- Two age peaks tend to be associated with different locations. Patients aged 2 to 6 years tend to have head and neck or genitourinary tract primary tumors, whereas adolescents aged 14 to 18 years tend to have primary tumors in extremities, truncal or paratesticular locations.
- Embryonal variety is most common in the first decade of life.
- Alveolar type is common in 11 to 26 years of age.
- Pleomorphic type occurs in adults over 40 years of age.
- Most common head and neck lesions are of embryonal and alveolar variety.
- Lesion occurs as a rapidly growing, painless and infiltrative mass.
- Common symptoms seen in patients are proptosis or dysconjugate gaze, painless scrotal mass, bladder or bowel difficulties, menorrhagia or metrorrhagia, protruding polypoid mass occurring in vagina also termed 'botryoid', meaning a grapelike cluster, upper respiratory symptoms or pain.
- Palate is the most frequent intraoral site.
- Several genetic syndromes and environmental factors are associated with increased prevalence of rhabdomyosarcoma.
- Genetic syndromes include the following:
 - Neurofibromatosis (4–5% risk of any one of numerous malignancies)
 - Li-Fraumeni syndrome (germline mutation of the tumor suppressor gene *TP53*)
 - Rubinstein-Taybi syndrome
 - Gorlin basal cell nevus syndrome
 - Beckwith-Wiedemann syndrome
 - Costello syndrome

- Environmental factors appear to influence the development of rhabdomyosarcoma, as follows:
 - Parental use of marijuana and cocaine
 - Intrauterine exposure to X-rays
 - Previous exposure to alkylating agents.

HISTOPATHOLOGIC FEATURES

- Lesional tissue in the well differentiated embryonic variety is composed of round to ovoid rhabdomyoblasts with eosinophilic cytoplasm and fibrillar material around the nucleus. Stout described rhabdomyoblasts as appearing in round, strap, racquet and spider forms. Rhabdomyoblasts sometimes have discernible muscle striations. In case of poorly-differentiated variety, cells are round or oval with nuclear hyperchromatism and indistinct cytoplasm. Botryoid variety of this type shows myxoid stroma (Fig. 9.21).
- Lesional tissue in alveolar variety is composed of round to ovoid rhabdomyoblasts with lack of cohesion and atypical mitosis. Numerous multinucleated giant cells are also evident.
- Lesional tissue in pleomorphic variety is composed of haphazardly arranged cluster of cells with cellular pleomorphism.

Management

Treatment in patients with rhabdomyosarcoma (RMS) involves a combination of surgery, chemotherapy, and radiation therapy.

SYNOVIAL SARCOMA

Synovial sarcomas represent 6 to 10 percent of all soft tissue sarcomas. Only 3 to 10 percent of synovial sarcomas arise in the head and neck.

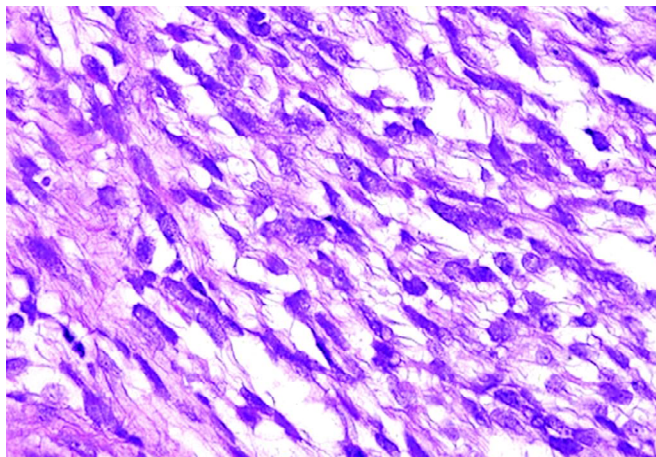


FIGURE 9.21: Histopathologic picture of rhabdomyosarcoma showing round to ovoid rhabdomyoblasts with eosinophilic cytoplasm

ETIOPATHOGENESIS

They do not arise from synovial tissue; rather, they originate from pluripotential mesenchymal cells and rarely occur within joint spaces. A reciprocal translocation, $t(X;18)(p11.2;q11.2)$ has been identified in monophasic and biphasic synovial sarcoma.

CLINICAL FEATURES

- Incidence of occurrence in teenagers and young adults is most common.
- Most commonly seen in males.
- The hypopharynx and retropharynx are the most common sites of involvement in the head and neck.
- The most common presentation is that of a painless mass; various associated symptoms may be present, depending on the location of the tumor.
- Calcifications are present in more than 50 percent of tumors and may be noted on radiography.

HISTOPATHOLOGIC FEATURES

- Three subtypes of synovial sarcoma are described: biphasic, monophasic, and poorly differentiated.
- Biphasic synovial sarcomas are composed of epithelioid and spindle cells (Fig. 9.22).
- Usually, the spindle cell component predominates.
- Mast cells, mitoses, areas of calcification and scant collagen production are typical of biphasic synovial sarcoma.
- The epithelioid cells form pseudoglandular cavities filled with mucin.
- Monophasic synovial sarcoma is composed of a single cellular type and may be derived from epithelioid or spindle cells. In either of the cases, spindle cells predominate.
- A rare poorly differentiated subtype has been described. These tumors may consist predominantly of epithelioid cells, spindle cells or a small cell variant that forms rosettes.

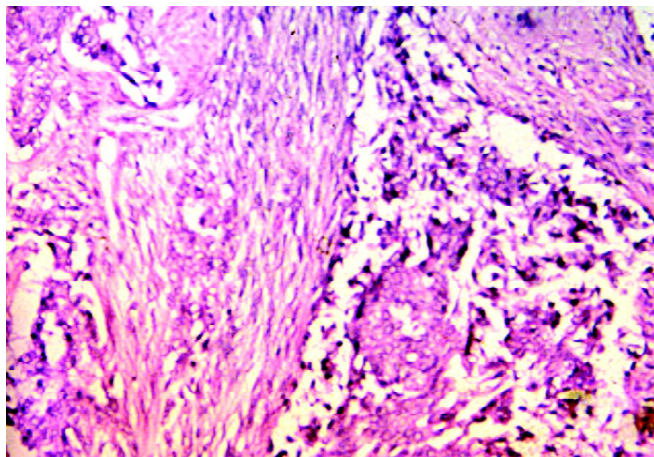


FIGURE 9.22: Histopathologic picture of biphasic synovial sarcoma composed of epithelioid and spindle cells

Management

1. Surgical excision combined with postoperative radiation therapy is the primary treatment for synovial sarcoma.
2. Chemotherapy with ifosfamide compounds appears to be of benefit in the treatment of distant metastases.

ALVEOLAR SOFT PART SARCOMA

Alveolar soft part sarcoma (ASPS) is a rare tumor, accounting for less than one percent of sarcomas. Head and neck involvement occurs in 27 percent of cases.

ETIOPATHOGENESIS

The origin of these tumors is unclear. Some authors suggest a neuroendocrine origin, citing evidence of myelinated axon formation within the lesion. Others support the idea of a myogenous origin for ASPS because of the presence of MyoD1, myogen, and desmin in many lesions. Mutation at the 17q25 site has been reported in ASPS, although the significance of this finding is unclear.

CLINICAL FEATURES

- Incidence of occurrence in young adults and children is more common.
- The most common sites for alveolar soft part sarcoma in the head and neck are the orbit and tongue.
- In comparison to older patients where the lesion occurs in extremities, the lesion is seen more frequently involving the head and neck region in children.
- Most commonly occurs in females in case of young patients.
- It occurs as a slow growing painless mass.
- Alveolar soft part sarcomas tend to be highly vascular and a bruit may be auscultated on examination.

HISTOPATHOLOGIC FEATURES

- The name alveolar soft part sarcoma is derived from its characteristic appearance at light microscopy, which is described as groups of epithelioid tumor cells in a highly vascular matrix.
- Grouped polygonal tumor cells with granular eosinophilic cytoplasm are arranged in an organoid configuration and separated by thin fibrovascular septa (Fig. 9.23).
- Central areas within these nests of cells become necrotic and the loss of architecture produces an alveolar appearance.
- Mitotic bodies are uncommon. Rhomboid and rod-shaped crystals are arranged in a sheaflike orientation in the cytoplasm of 75 percent of tumors.

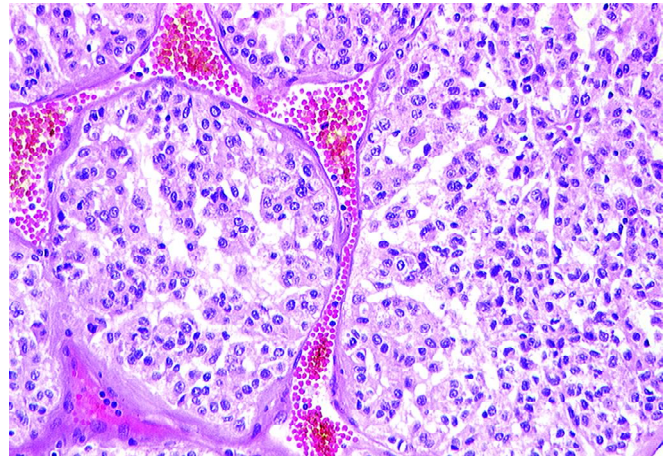


FIGURE 9.23: Histopathologic picture of alveolar soft part sarcoma showing grouped polygonal tumor cells with granular eosinophilic cytoplasm

Management

1. Surgical excision is the treatment of choice; elective neck dissection is not indicated because of the low incidence of cervical metastases.
2. Adjuvant radiation therapy or chemotherapy has not been shown to provide any improvement in disease control or survival.

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Bone Pathology in Children

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CHAPTER OVERVIEW

Introduction
 Osteogenesis imperfecta (OI)
 Osteopetrosis
 Cleidocranial dysplasia
 Cherubism
 Fibrous dysplasia
 Chondromyxoid fibroma (CMF)
 Familial gigantiform cementoma
 Juvenile ossifying fibroma (JOF)
 Marfan syndrome
 Achondrogenesis
 Chondrodysplasia punctata
 Pycnodysostosis
 Mucopolysaccharidosis
 Rickets
 Hyperparathyroidism
 Hypoparathyroidism
 Craniosynostosis syndromes
 Craniofacial dysostosis – Crouzon syndrome
 Mandibulofacial dysostosis – Treacher collins syndrome
 Franceschetti syndrome

Pierre Robbin syndrome
 Apert syndrome
 Thanatophoric dysplasia
 Achondroplasia
 Robinow syndrome
 Hyperostosis corticalis generalisata
 Chondroectodermal dysplasia
 Trichodonto-osseous syndrome
 Down's syndrome
 Infantile cortical hyperostosis
 Massive osteolysis
 Cementoblastoma
 TMJ abnormalities:
 Aplasia of mandibular condyle
 Hypoplasia of mandibular condyle
 Hyperplasia of mandibular condyle
 Ankylosis
 Langerhans cell histiocytosis
 Hand-Schüller-Christian disease
 Eosinophilic granuloma

INTRODUCTION

Bone is a specialized connective tissue and consists of cells, fibers and extracellular matrix. This matrix gets ossified and forms hard structure i.e. bone. Bone formation takes place by endochondral and intramembranous ossification. Its main functions are protection of internal structures, hemopoiesis and it also serves as a reservoir for calcium, phosphate and other minerals. Any impairment in the structure and function of bone which may be due to one or other cause leads to pathological conditions of bone. This chapter focuses on some of the bone pathologies pertaining to children.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI) comprises of hereditary disorders characterized by impairment of collagen maturation and arises

from mutation on genes *COL1A1* on chromosome 17 and *COL1A2* on chromosome 7 that guide formation of collagen type 1. Type I collagen fibers are found in the bones, organ capsules, fascia, cornea, sclera, tendons, meninges, and dermis. Type I collagen, which constitutes approximately 30 percent of the human body by weight, is the defective protein in OI. This results in bone with a thin cortex, fine trabeculation and diffuse osteoporosis.

CLINICAL FEATURES

- Affects 1 in 20,000 individuals.
- Occurs as autosomal dominant and recessive hereditary patterns.
- The age when symptoms (i.e. fractures) begin widely varies. Patients with mild forms may not have fractures until

TABLE 10.1: Conditions in which blue sclera is seen

Blue sclera may also be seen in other conditions like:

- Progeria
- Cleidocranial dysplasia
- Menkes syndrome
- Cutis laxa
- Cheney syndrome
- Pyknodysostosis.

adulthood or patients may present with fractures in infancy. Patients with severe forms present with fractures *in utero* also.

- Common symptoms of blue sclera, altered teeth, hearing loss, and long bone and spine deformities are seen in affected individuals.
- Patients most commonly present with fractures after minor trauma.
- Patients may bruise easily.
- Other conditions in which blue sclera is seen have been mentioned in Table 10.1.
- Four major types of osteogenesis imperfecta have been reported:

Type I OI— Mild Forms

- Patients have no long-bone deformity.
- The sclera can be blue or white.
- Dentinogenesis imperfecta may be present.
- Over a lifetime, the number of fractures can range from 1 to 60.
- Height is usually normal in individuals with mild forms of OI.
- People with OI have a high tolerance for pain. Old fractures can be discovered in infants when radiographs are obtained for reasons other than an assessment of OI, and they can occur without any signs of pain.
- Exercise tolerance and muscle strength are significantly reduced in patients with OI, even in the mild forms.
- Fractures are most common during infancy but may occur at any age.
- Other possible findings include kyphoscoliosis, hearing loss, premature arcus senilis, and easy bruising.

Type II—Extremely Severe

- Type II is often lethal.
- Blue sclera may be present (Fig. 10.1).
- Patients may have a small nose, micrognathia, or both.
- All patients have *in utero* fractures, which may involve the skull, long bones, and/or vertebrae.
- The ribs are beaded and the long bones are severely deformed.
- Causes of death include extreme fragility of the ribs, pulmonary hypoplasia, and malformations or hemorrhages of the CNS.



FIGURE 10.1: Osteogenesis imperfecta showing blue sclera

Type III—Severe

- Patients may have joint hyperlaxity, muscle weakness, chronic unremitting bone pain, and skull deformities (e.g. posterior flattening) due to bone fragility during infancy.
- Deformities of upper limbs may compromise function and mobility.
- The presence of dentinogenesis imperfecta is independent of the severity of OI.
- The sclera has variable hues.
- *In utero* fractures are common.
- Limb shortening and progressive deformities can occur.
- Patients may have a triangular face with frontal bossing.
- Basilar invagination is an uncommon but potentially fatal occurrence in OI.
- Vertigo is common in patients with severe OI.
- The incidence of congenital malformations of the heart in children with OI is probably similar to that of the healthy population.
- Hypercalciuria may be present in about 36 percent of patients with OI but does not appear to affect renal function.
- Respiratory complications secondary to kyphoscoliosis are common in individuals with severe OI.
- Constipation and hernias are also common in people with OI.

Type IV—Undefined

- This type of OI is not clearly defined.
- Whether patient has normal height or whether scleral hue defines the type has not been established in consensus.
- Dentinogenesis imperfecta may be present. Some have suggested that this sign can be used to divide type IV OI into subtypes a and b.
- Fractures usually begin in infancy, but *in utero* fractures may occur. The long bones are usually bowed (Figs 10.2 and 10.3).



FIGURE 10.2: Osteogenesis imperfecta showing bowing of leg



FIGURE 10.3: Osteogenesis imperfecta showing bowing of legs due to formation of immature bone

RADIOGRAPHIC FEATURES

- Deformity and multiple fractures of long bones along with the formation of wormian bones (immature bones arranged haphazardly) in the skull.
- Premature pulpal obliteration is seen in both primary and permanent dentitions.
- On occasion, may show mixed radiolucencies.

HISTOPATHOLOGIC FEATURES

- Reduction in bone matrix production
- Failure of woven bone to become lamellar bone

Management

1. Since osteogenesis imperfecta (OI) is a genetic condition, it has no cure.
2. Cyclic administration of intravenous pamidronate reduces the incidence of fracture and increases bone mineral density, while reducing pain and increasing energy levels.¹ Doses vary from 4.5 to 9 mg/kg/y, depending on the protocol used.
3. Current evidence does not support the use of oral bisphosphonates in patients with OI.
4. Nutritional evaluation and intervention are paramount to ensure appropriate intake of calcium and vitamin D. Caloric management is important, particularly in adolescents and adults with severe forms of OI.
5. Orthopedic surgery is one of the pillars of treatment for patients with OI. Surgical interventions include intramedullary rod placement, surgery to manage basilar impression, and correction of scoliosis.
6. Surgery for basilar impression is reserved for cases with neurologic deficiencies, especially those caused by compression of brainstem and high cervical cord. A team of orthopedic surgeons and neurosurgeons is required.
7. Correction of scoliosis may be difficult because of bone fragility. Spinal fusion may be helpful. Pretreatment with pamidronate appears to improve the surgical outcome.

OSTEOPETROSIS

Osteopetrosis was first described by a German radiologist, **Albers-Schönberg** in 1904.² It is a clinical syndrome characterized by the failure of osteoclasts to resorb bone.

Osteoclasts are derived from the monocyte/macrophage lineage. Osteoclasts can tightly attach to the bone matrix by integrin receptors to form a sealing zone, within which a sequestered compartment is acidified. Acidification promotes solubilization of the bone mineral in the sealing zone, and various proteases, notably cathepsin K, catalyze degradation of the matrix proteins.

Bone modeling and remodeling differ in that, modeling implies a change in the shape of the overall bone and is prominent during childhood and adolescence. Modeling is the process by which the marrow cavity expands as the bone grows in length and diameter. Failure of modeling is the basis of hematopoietic failure in osteopetrosis. Remodeling, in contrast, involves the degradation of bone tissue from a preexisting bony structure and replacement of the degraded bone by newly synthesized bone. Failure of remodeling is the basis of the persistence of primary spongiosa and woven bone.

The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also

TABLE 10.2: Clinical classification of human osteopetrosis

Characteristic	Adult onset	Infantile	Intermediate
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Bone marrow failure	None	Severe	None
Prognosis	Good	Poor	Poor
Diagnosis	Often diagnosed incidentally	Usually diagnosed before age 1 year	Not applicable

cause hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes and growth impairment.

CLINICAL FEATURES

- Three variants of the disease are diagnosed in infancy, childhood (intermediate), or adulthood (Table 10.2).
- Infantile osteopetrosis (also called malignant osteopetrosis) is diagnosed early in life (Fig. 10.4).
- Failure to thrive and growth retardation are symptoms.
- Bony defects occur. Nasal stuffiness due to mastoid and paranasal sinus malformation is often the presenting feature of infantile osteopetrosis. Neuropathies related to cranial nerve entrapment occur due to failure of the foramina in the skull to widen completely. Manifestations include deafness, proptosis, and hydrocephalus. Dentition might be delayed (Fig. 10.5). Osteomyelitis of the mandible is common due to an abnormal blood supply. Bones are fragile and can fracture easily.
- Defective osseous tissue tends to replace bone marrow, which can cause bone marrow failure with resultant pancytopenia. Patients might have anemia, easy bruising and bleeding (due to thrombocytopenia), and recurrent infections (due to inherent defects in the immune system). Extramedullary hematopoiesis might occur with resultant hepatosplenomegaly, hypersplenism, and hemolysis.
- Other manifestations include sleep apnea and blindness due to retinal degeneration.
- Adult osteopetrosis (also called benign osteopetrosis) is diagnosed in late adolescence or adulthood.
- Two distinct types have been described, type I and type II, on the basis of radiographic, biochemical, and clinical features.³ (Table 10.3)
- Recent work has demonstrated that the clinical syndrome of adult type I osteopetrosis is not true osteopetrosis, but rather, increased bone mass due to activating mutations of *LRP5*.⁴
- Some cases of type II osteopetrosis result from mutations of *CLCN7*, the type 7 chloride channel.⁵



FIGURE 10.4: Infantile osteopetrosis

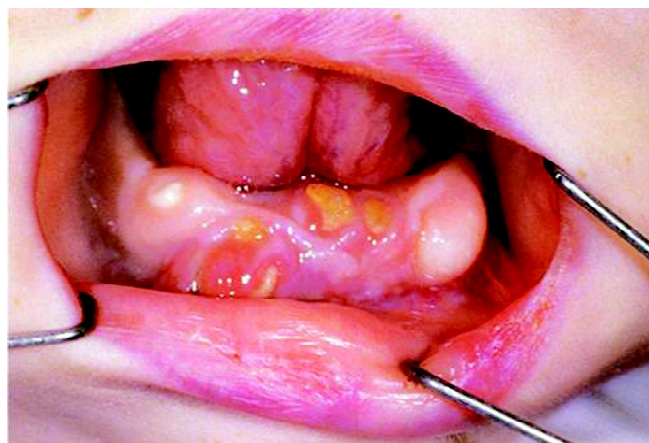


FIGURE 10.5: Infantile osteopetrosis showing absence of teeth due to delayed eruption

TABLE 10.3: Characteristic differences between Type I and Type II osteopetrosis

Characteristic	Type I	Type II
Skull sclerosis	Marked sclerosis mainly of the vault	Sclerosis mainly of the base
Spine	Does not show much sclerosis	Shows the "rugger-jersey appearance"
Pelvis	No endobones	Shows endobones in the pelvis
Transverse banding of metaphysis	Absent	May or may not be present
Risk of fracture	Low	High
Serum acid phosphatase	Normal	Very high

- Many patients have bone pains. Bony defects are common and include neuropathies due to cranial nerve entrapment (e.g.: with deafness, with facial palsy), carpal tunnel syndrome, and osteoarthritis. Bones are fragile and might fracture easily. Approximately 40 percent of patients have recurrent fractures. Osteomyelitis of the mandible occurs in 10 percent of patients.
- Bone marrow function is not compromised.
- Other manifestations include visual impairment due to retinal degeneration and psychomotor retardation.

RADIOGRAPHIC FEATURES

Patients generally show osteosclerosis. Sclerotic areas may be noted at the ends of long bones (Figs 10.6A and B). Thickening of skull at the base is seen. Due to brittleness of bones, sometimes fractures are noted; density of jaw may be reduced such that the roots of the teeth are visible.

HISTOPATHOLOGIC FEATURES

- Lesional area is comprised of irregular, lamellar trabeculae replacing the cancellous portion of the bone.
- Globular amorphous bone deposition in the marrow spaces.
- Osteophytic bone formation.

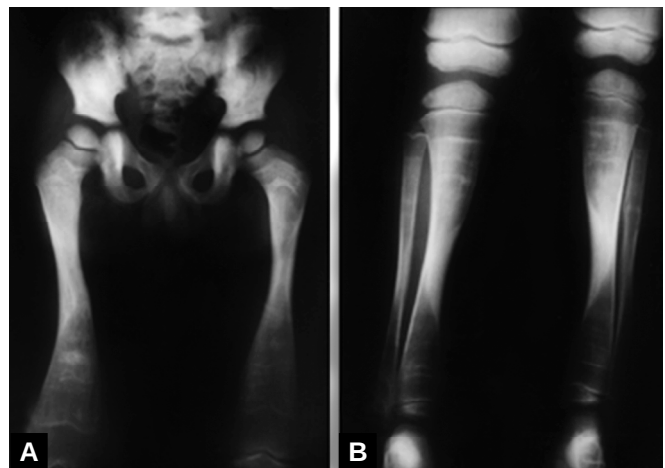
Management

1. Infantile osteopetrosis warrants treatment because of the adverse outcome associated with the disease.
2. Vitamin D (calcitriol) appears to help by stimulating dormant osteoclasts and thus stimulate bone resorption. Large doses of calcitriol, along with restricted calcium intake, sometimes improve osteopetrosis dramatically.⁶ It usually produces only modest clinical improvement, which is not sustained after therapy is discontinued.

3. Treatment with gamma interferon has produced long-term benefits. It improves WBC function, tremendously decreasing the incidence of new infections. With treatment, trabecular bone volume substantially decreases, and bone-marrow volume increases. This effects increase in hemoglobin, platelet counts, and survival rates. Combination therapy with calcitriol is clearly superior to calcitriol alone.
4. Erythropoietin can be used to correct anemia.
5. Corticosteroids have been used to stimulate bone resorption and treat anemia. Prednisone 1–2 mg/kg/day is usually administered for months to years. Steroids are not the preferred treatment option.
6. Adult osteopetrosis requires no treatment by itself, though complications of the disease might require intervention. No specific medical treatment exists for the adult type.
7. Bone marrow transplant (BMT) markedly improves some cases of infantile osteopetrosis.
8. In pediatric osteopetrosis, surgical treatment is sometimes necessary because of fractures.
9. In adult osteopetrosis, surgical treatment may be needed for aesthetic reasons (e.g. in patients with notable facial deformity) or for functional reasons (e.g. in patients with multiple fractures, deformity, and loss of function). Severe, related degenerative joint disease may warrant surgical intervention as well.

CLEIDOCRANIAL DYSPLASIA

It is basically a disorder that primarily affects the development of the bones and teeth. It is caused by a defect in CBFA 1 gene of chromosome 6p21 that normally guides osteoblastic differentiation and appropriate bone formation. It usually affects membranous bone (clavicle, skull and flat bones). Recently it has been shown to affect endochondral bone. It shows autosomal dominant pattern.



FIGURES 10.6 A and B: Infantile osteopetrosis showing sclerosis at the end of long bones

CLINICAL FEATURES

- Patients suffering from this disorder show short, tapered fingers and broad thumbs.
- Short forearms, flat feet, knock knees.
- An abnormal curvature of the spine (scoliosis).
- A wide, short skull (brachycephaly) and a prominent forehead.
- Wide-set eyes (hypertelorism).
- A flat nose and a small upper jaw.
- Delayed loss of the primary teeth.
- Delayed appearance of the permanent (adult) teeth.
- Unusually shaped, peg-like teeth.
- Misalignment of the teeth and jaws (malocclusion).
- Supernumerary teeth, sometimes accompanied by cysts in the gingiva (Fig. 10.7).
- Hearing loss, and sinus and ear infections.
- Some young children with this condition are mildly delayed in the development of motor skills such as crawling and walking, but intelligence is unaffected.
- Hypermobility of shoulders is seen in some children (Fig. 10.8).

RADIOGRAPHIC FEATURES

- Skull radiographs show delayed closure of sutures and fontanelles may remain open throughout patient's life.
- Mandible shows area of increased density, narrow ascending rami and slender pointed coronoid process.
- Maxilla shows thin zygomatic arch and small or absent maxillary sinuses.
- Chest radiographs may show absence of clavicles (Fig. 10.9).

HISTOPATHOLOGIC FEATURES

Microscopic examination of unerupted permanent teeth reveals lack of secondary cementum.

Management

1. One or more of the treatment modalities may be followed depending upon the extent of malformation.
2. Extensive orthodontic treatment for functional alignment of the teeth.
3. Full mouth extractions followed by placement of dentures.
4. Autotransplant of selected impacted teeth followed by prosthetic restoration.
5. Removal of primary and supernumerary teeth followed by exposure of permanent teeth.

CENTRAL GIANT CELL GRANULOMA

Reactive condition thought to be due to organization of slow, minute, recurrent hemorrhages, characterized by osteoclast-like

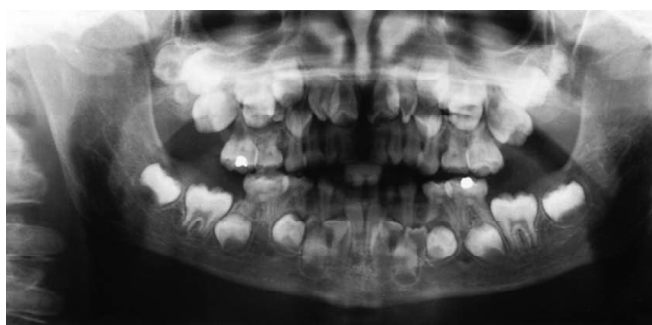


FIGURE 10.7: Cleidocranial dysplasia showing numerous unerupted and supernumerary teeth



FIGURE 10.8: Cleidocranial dysplasia showing hypermobility of shoulder



FIGURE 10.9: Cleidocranial dysplasia showing complete absence of clavicles

multinucleated giant cells with vascular stroma and new bone formation. The World Health Organization has defined central giant cell granuloma as an intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone.⁷

CLINICAL FEATURES

- Incidence of occurrence at 2 to 70 years is most common.
- Occurs most commonly in females.
- Most commonly seen in the anterior region of mandible, most often crossing the midline.
- They are classified on the basis of radiographic and clinical features as:
 - Nonaggressive lesions: Slow growing, asymptomatic and do not show cortical perforation or root resorption of associated teeth.⁸
 - Aggressive lesions: Found in young patients and characterized by rapid growth, pain, cortical perforation and root resorption and marked tendency to recur.⁹

RADIOGRAPHIC FEATURES

Lesion appears as a well demarcated, unilocular or multilocular radiolucent defect (Fig. 10.10).

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows proliferating endothelial cells, numerous small capillaries, multinucleated giant cells and active fibroblasts and myofibroblasts embedded in fibrous stroma (Fig. 10.11).
- Few studies suggest that multinucleated giant cells represent osteoclasts.
- Areas of hemorrhage are evident.
- Younger lesions mature over a period of time and become fibrous.

Management

1. Thorough curettage.
2. Aggressive tumors are treated by either administration of corticosteroids, calcitonin and interferon alpha-2a.
3. Injections of triamcinolone acetonide for six weeks into the tumor have been used successfully.

CHERUBISM

Cherubism is a benign disease with a characteristic symmetrical involvement of the maxilla and mandible. It was first described by Jones in 1933 as a “familial multilocular disease of the jaws” in three siblings who appeared as though they were “looking towards heaven”. This inspired him to call the condition

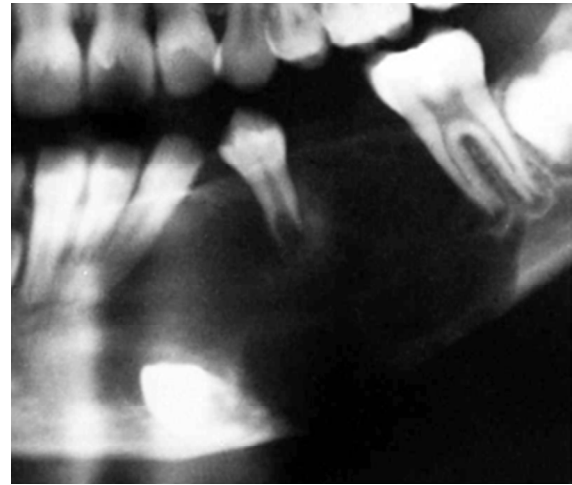


FIGURE 10.10: Central giant cell granuloma showing large unilocular radiolucent area in posterior mandible

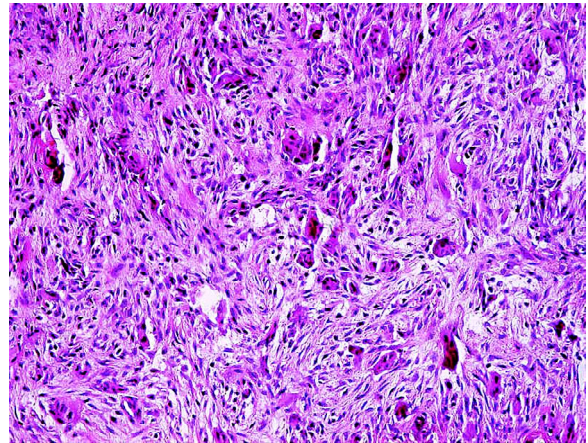


FIGURE 10.11: Histopathologic picture of central giant cell granuloma showing multinucleated giant cells and active fibroblasts

“cherubism”, to describe the round appearance of the cheeks, typical of cherubs, resulting from jaw hypertrophy.¹⁰ Mutations in the SH3BP2 gene have been identified in about 80 percent of people with cherubism. The gene responsible for cherubism was recently mapped to the chromosome 4p16.3.

CLINICAL FEATURES

- Cherubism is a disease of childhood that usually presents before the age of five, most often between 12 and 36 months.
- Males are affected more commonly than females.
- Wide rim of exposed sclera is noted below the iris, therefore called ‘eye to heaven’ appearance (Figs 10.12A and B).
- Mandibular lesions appear as painless, bilateral expansion of the posterior mandible that tends to involve angles and ascending rami.



FIGURES 10.12A and B: Cherubism showing eye to heaven appearance

- Maxillary involvement is rare but if it occurs, it mainly affects the tuberosity area.
- Displacement or failure of eruption of tooth, speech difficulty, loss of normal vision or hearing.

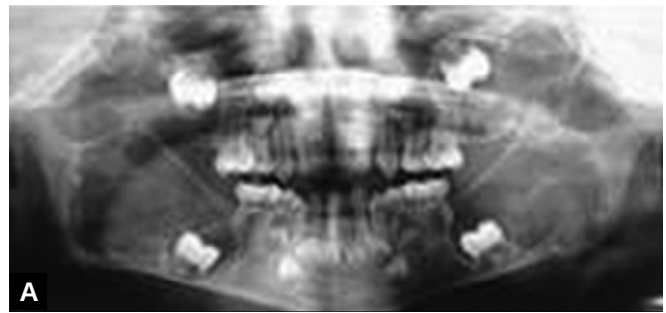
RADIOGRAPHIC FEATURES

- Unilocular or multilocular radiolucencies of the jaw.
- Most of the cases show bilateral radiolucencies (Figs 10.13A and B).

CT scans showing expansile remodeling, cortical thinning, and multilocular contour with coarse trabecular pattern. Maxillary disease resulting in dental derangement is also seen.

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows vascular fibrous connective tissue with variable number of multinucleated giant cells and spindle shaped cells (Fig. 10.14).
- Eosinophilic, cufflike deposits surrounding small blood vessels are the characteristic features of this lesion.



FIGURES 10.13A and B: Cherubism showing bilateral involvement of mandible

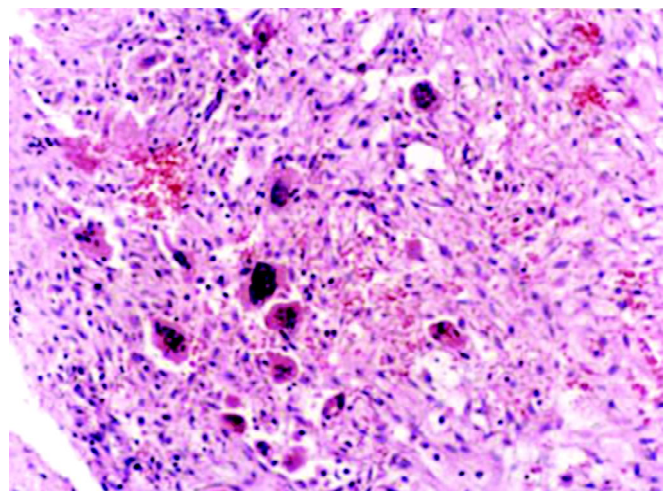


FIGURE 10.14: Histopathologic picture of cherubism showing cellular fibrous mass with interspersed multinucleated giant cells

- Older lesions appear more fibrous and there is a decrease in the number of giant cells.

Management

1. Early surgical intervention with curettage of the lesions. But rapid regrowth of the lesions is a potential complication.
2. Use of calcitonin in severe cases has been suggested.
3. Radiotherapy is contraindicated because of risk of development of post irradiation sarcoma.

FIBROUS DYSPLASIA

The term fibrous dysplasia was first mentioned by Lichtenstein in 1938.¹¹ It is a rare localised disease often associated with bony deformities caused by the abnormal proliferation of fibrous tissue interspersed with normal or immature bone because of poorly differentiated, mutated osteoblasts. Some authors suggest that greater resorption of bone in affected areas is because of the activation of Gs 1 and increased synthesis of IL6, a cytokine involved in the differentiation of osteoclasts.¹²

Two types of fibrous dysplasia are as follows:

1. Monostotic: When only one bone is involved.
2. Polyostotic: When multiple bones are involved. Occurs along with cutaneous and endocrine abnormalities.

MONOSTOTIC FIBROUS DYSPLASIA

- Occurs in childhood.
- Higher incidence of occurrence in males.
- Occurrence in maxilla is more common than mandible.
- There occurs painless bulging of the jaw.
- Tipping or displacement of teeth is evident.
- When occurs in maxilla along with other bones, it is termed as '*craniofacial fibrous dysplasia*'. This form is most common in children (Fig. 10.15).

RADIOGRAPHIC FEATURES (FIG. 10.16)

Ground glass appearance due to collection of poorly calcified bony trabeculae arranged in disorganized pattern.

POLYOSTOTIC FIBROUS DYSPLASIA

- It is usually less common.
- Mostly occurs unilaterally.
- When combined with cutaneous abnormalities (*café au lait*=coffee with milk) pigmentation—termed as Jaffe Lichtenstein syndrome.
- Polyostotic fibrous dysplasia, when occurs along with *café au lait* spots and endocrine abnormalities, is termed as McCune-Albright syndrome.

HISTOPATHOLOGIC FEATURES

- Lesional tissue shows irregular shaped trabeculae of immature bone in cellular, loosely arranged fibrous stroma.



FIGURE 10.15: Craniofacial fibrous dysplasia showing distortion of the face

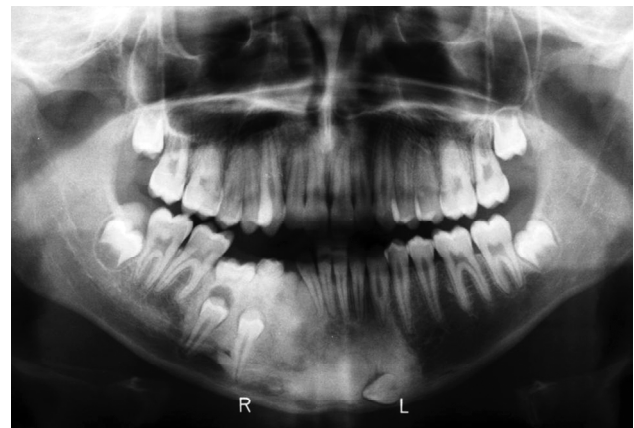


FIGURE 10.16: Craniofacial fibrous dysplasia showing ground glass appearance of the bony trabeculae

- The bony trabeculae often assume curvilinear shape termed as "*Chinese letter pattern*" (Fig. 10.17).
- These trabeculae are lined by osteoblasts.

Management

1. Resection cures fibrous dysplasia in bones such as ribs.
2. Curettage is adequate in long bones such as tibia.
3. Partial removal in maxilla which may resolve some of the deformity.
4. Pamidronate 60 mg/day given intravenously on three successive days to reduce osteoclastic activity has been given every 6 months for 18 months. It resulted in a decreased intensity of bony pain, reduced bony resorption, and improved radiological features such as filling of lytic lesions in about half the patients. But such treatment modality had not been tried yet in children.¹³

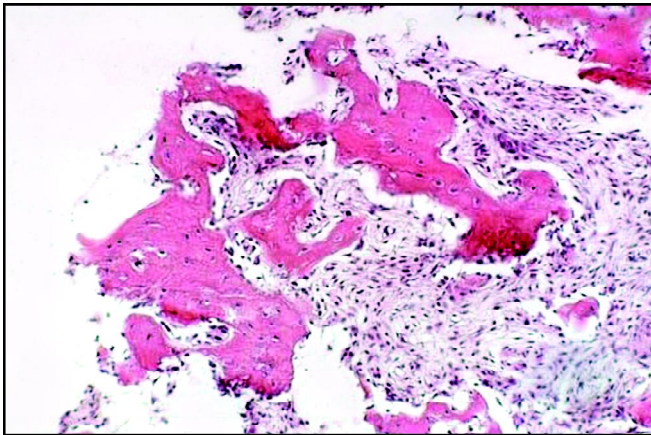


FIGURE 10.17: Histopathologic picture of craniofacial fibrous dysplasia showing “Chinese letter pattern”

CHONDROMYXOID FIBROMA

Chondromyxoid fibroma (CMF) is a rare, slow-growing bone tumor of chondroblastic derivation. Jaffe and Lichtenstein first described the condition in 1943.¹⁴ In a study of four patients with CMF, Granter and colleagues found that all of the subjects had a clonal rearrangement of chromosome 6. Each of these rearrangements involved band 6q13, which has not been associated with other bone tumors.¹⁵

CLINICAL FEATURES

- Males and females are affected equally.
- Incidence of occurrence is common in the age range of 3 to 87 years.
- Pain and swelling are common symptoms.
- The proximal tibia is the most common location, followed by the distal femur, pelvis, and foot. Long bones are involved much more frequently than are other bones, especially in younger patients.¹⁶
- Rarely is an involvement of the jaw seen.

RADIOGRAPHIC FEATURES (FIG. 10.18)

Well circumscribed radiolucent lesion with scalloped margins is seen. Sometimes there is presence of radiopacities within the lesion.

HISTOPATHOLOGIC FEATURES (FIGS 10.19 AND 10.20)

- Lesional tissue shows lobules of spindle shaped cells surrounded by myxoid stroma.
- Sometimes multi-nucleated giant cells are visible within the stroma.
- Low power view shows a moderately cellular chondromyxoid tissue with the following two characteristic features:
 1. Vague lobularity caused by alternating highly cellular and less cellular areas;
 2. Increased cellularity at the periphery of the lobules.

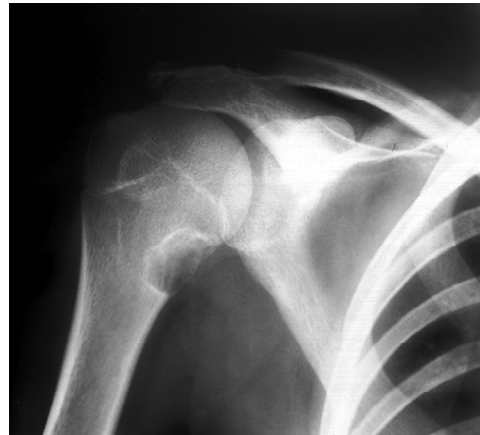


FIGURE 10.18: Chondromyxoid fibroma showing well circumscribed radiolucent lesion

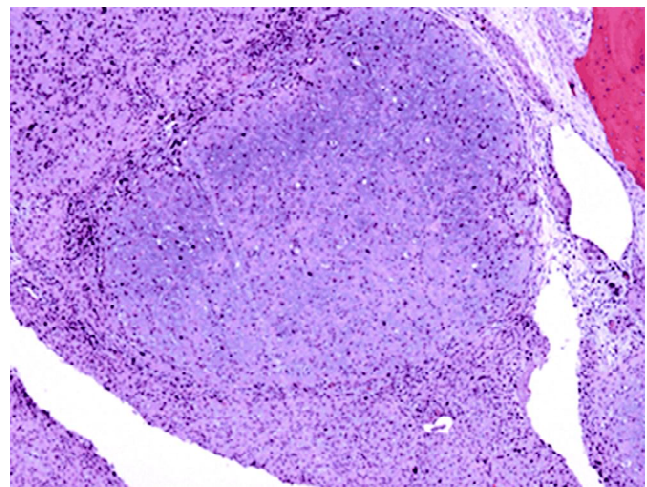


FIGURE 10.19: Histopathologic picture of chondromyxoid fibroma showing vague lobularity caused by alternating highly cellular and less cellular areas

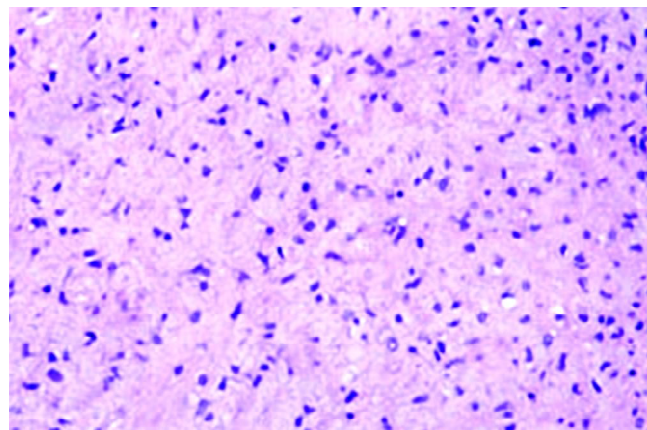


FIGURE 10.20: Histopathologic picture of chondromyxoid fibroma showing mildly pleomorphic, angular and stellate cells set in bluish-pink chondromyxoid stroma

Higher magnification view of the lobule shows mildly pleomorphic, angular and stellate cells set in bluish-pink chondromyxoid stroma. Note that the tumor lacks true hyaline cartilage matrix seen in chondromas and chondrosarcomas. Another important feature is lack of mitotic activity.

Management

1. Nonsteroidal anti-inflammatory agents or analgesics may be beneficial for pain control.
2. CMFs are treated with intralesional curettage or *en bloc* excision.¹⁷

FAMILIAL GIGANTIFORM CEMENTOMA

Gigantiform cementoma (GC) was first reported in 1930 by **Norberg** to describe a condition characterized by diffuse radiopaque masses scattered throughout the jaws.¹⁸ These masses frequently caused expansion. In 1953, **Agazzi and Belloni** described an Italian family in which several members were affected, and this was designated Familial gigantiform cementoma (FGC) or familial multiple cementomas.¹⁹

CLINICAL FEATURES

- It occurs as an autosomal dominant disorder.
- Shows no sex predilection.
- Incidence of occurrence is common during first decade of life.
- Both maxilla and mandible are equally involved.
- It occurs as an expansile lesion which results in facial deformity and malocclusion.

RADIOGRAPHIC FEATURES

Radiographic features are variable from radiolucent to mixed features to radiopaque as the lesion matures.

HISTOPATHOLOGIC FEATURES

- Lesional tissue is composed of mature connective tissue stroma showing fibroblasts and collagen fibers.
- These components surround bony trabeculae and mostly cementum-like material.
- Numerous blood vessels are also evident.
- As the lesion matures, connective tissue component decreases and cemento-osseous component dominates.

Management

- Wide surgical resection of the lesional area and reconstruction of facial skeleton and associated structures has been recommended.

JUVENILE OSSIFYING FIBROMA

Juvenile ossifying fibroma (JOF) is a rare fibro-osseous neoplasm that arises within the craniofacial bones in individuals under 15 years of age.

CLINICAL FEATURES

- They occur in two forms, viz. trabecular and psammomatoid, as seen radiographically.
- JOF is often seen in a very young child. In reviews published by **Hamner et al**²⁰ and **Slootweg et al**²¹, the mean age of onset was 11.5 and 11.8 years old respectively, for the trabecular variety. The psammomatoid variety occurs at almost twice the age that of the trabecular variety.
- Lesion shows no sex predilection.
- The first clinical manifestation is a swelling of the maxilla.
- When the orbital bone and paranasal sinuses are involved as seen most of the times in psammomatoid variety, the patients may develop exophthalmos, bulbar displacement and nasal obstruction.

RADIOGRAPHIC FEATURES

- The radiographic features are variable and depend on the tumor's location and the amount of calcified tissue produced by the tumor.
- Thus the lesion will show varying degrees of radiolucency.

HISTOPATHOLOGIC FEATURES

- Lesional tissue is basically composed of loose fibrous connective tissue stroma interspersed with numerous bony trabeculae.
- Trabecular variety shows trabeculae of immature bone surrounded by fibrocellular connective tissue stroma. Trabeculae are lined by osteoblasts and osteoclasts and contain osteocytes.
- Psammomatoid variety shows numerous spherical ossicles with basophilic centers and peripheral eosinophilic rims surrounded by fibrocellular connective tissue stroma (Fig. 10.21).

Management

1. Complete local excision.
2. Thorough curettage.
3. Wide local excision for rapidly growing tumors.

MARFAN SYNDROME (FIGS 10.22A AND B)

Marfan syndrome is a heritable condition that affects the connective tissue. The primary purpose of connective tissue is to hold the body together and provide a framework for growth

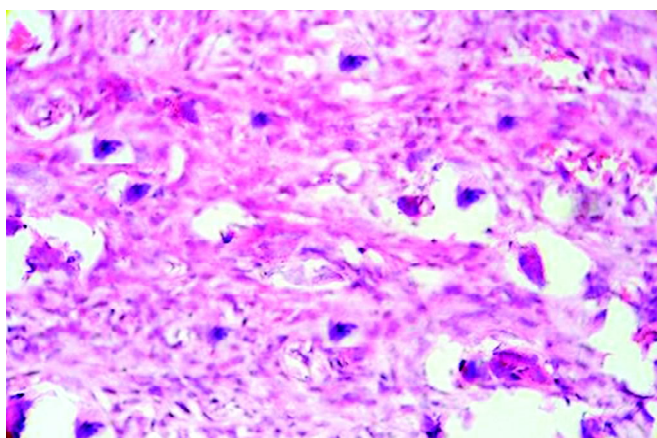
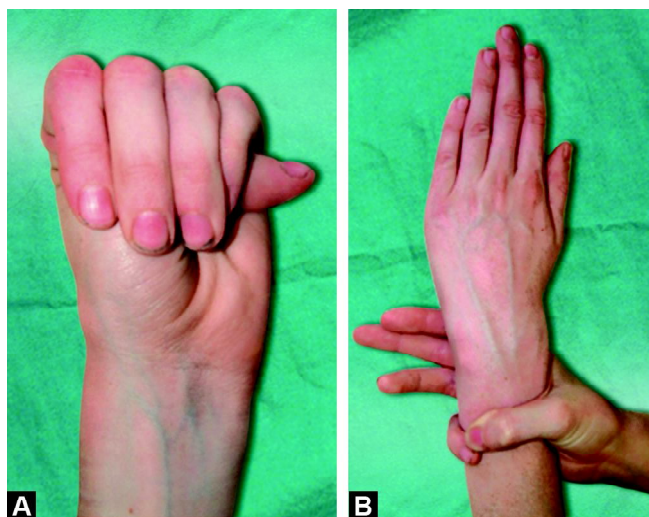


FIGURE 10.21: Histopathologic picture of juvenile ossifying fibroma showing spherical ossicles with basophilic centers



FIGURES 10.22A and B: Marfan syndrome showing arachnodactyly (a) positive thumb sign: entire thumbnail protrudes beyond ulnar border of hand. (b) Positive wrist sign: thumb and fifth finger overlap when encircling the wrist

and development. Because connective tissue is found throughout the body, Marfan syndrome can affect many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs.

Marfan syndrome is caused by a mutation in the gene *FBN1* on chromosome 15, bands *q15 to q23*, that determines the structure of fibrillin, a protein that is an important part of connective tissue. A person with Marfan syndrome is born with the disorder, even though it may not be diagnosed until later in life. Although everyone with Marfan syndrome has a defect in the same gene, variable expression is seen, meaning that the defective gene expresses itself in different ways in different people. The child of a person who has Marfan syndrome has a 50 percent chance of inheriting the disease, but two unaffected

parents have only a one in 10,000 chance of having a child with Marfan syndrome. Possibly 25 percent of cases are due to a spontaneous mutation at the time of conception.

CLINICAL FEATURES

Some people affected with Marfan syndrome have only mild symptoms, while others are more severely affected. In most cases, the symptoms progress as the person ages. The body systems most often affected by Marfan syndrome are:

- **Oral manifestations**—*Baden and Spirgi, 1965*, reviewed oral manifestations of Marfan syndrome and reported that a high arched palatal vault was the most common finding. Other oral manifestations are bifid uvula, malocclusion, multiple odontogenic cysts of maxilla and mandible and temporomandibular joint dysarthrosis.²²
- **Skeleton**—People with Marfan syndrome are typically very tall, slender, and loose jointed. Since Marfan syndrome affects the long bones of the skeleton, arms, legs, fingers, and toes may be disproportionately long in relation to the rest of the body. A person with Marfan syndrome often has a long, narrow face, and the roof of the mouth may be arched, causing the teeth to be crowded. Other skeletal abnormalities include a sternum (breastbone) that is either protruding or indented, curvature of the spine (scoliosis), and flat feet.
- **Eyes**—More than half of all people with Marfan syndrome experience dislocation of one or both lenses of the eye. The lens may be slightly higher or lower than normal and may be shifted off to one side. The dislocation may be minimal, or it may be pronounced and obvious. Retinal detachment is a possible serious complication of this disorder. Many people with Marfan syndrome are also myopic, and some can develop early glaucoma or cataracts.
- **Cardiovascular system**—Most people with Marfan syndrome have abnormalities associated with the heart and blood vessels. Because of faulty connective tissue, the wall of the aorta may be weakened and stretched, a process called aortic dilatation. Aortic dilatation increases the risk of aortic dissection or rupture, causing serious heart problems or sometimes sudden death. Sometimes, defects in heart valves can also cause problems creating ‘murmurs’. Small leaks may not result in any symptoms, but larger ones may cause shortness of breath, fatigue, and palpitations.
- **Nervous system**—The brain and spinal cord are surrounded by fluid contained in the dura, which is composed of connective tissue. As people with Marfan syndrome get older, the dura often weakens and stretches, then begins to weigh on the vertebrae in the lower spine and wear away the bone surrounding the spinal cord. This is called dural ectasia. These changes may cause only mild discomfort or may lead to radiating pain in the abdomen or pain, numbness, or weakness of the legs.

- **Skin**—Many people with Marfan syndrome develop stretch marks on their skin, even without any weight change. These stretch marks can occur at any age and pose no health risk. However, people with Marfan syndrome are also at increased risk for developing an abdominal or inguinal hernia.
- **Lungs**—Although connective tissue abnormalities make the pulmonary alveoli less elastic, people with Marfan syndrome generally do not experience noticeable problems with their lungs. However, the risk of lung collapse may be present. Rarely, people with Marfan syndrome may have sleep-related breathing disorders such as snoring or sleep apnea.

DIAGNOSIS

There is no specific laboratory test, such as a blood test or skin biopsy, to diagnose Marfan syndrome. The doctor and/or geneticist relies on observation and a complete medical history, including:

- Information about any family members who may have the disorder or who had an early, unexplained heart-related death.
- A thorough physical examination, including an evaluation of the skeletal frame for the ratio of arm/leg size to trunk size.
- An eye examination, including a “slit lamp” evaluation.
- Heart tests such as an echocardiogram.

Management

1. There is no cure for Marfan syndrome. Scientists are trying to identify and change the specific gene responsible for the disorder before birth.
2. Orthodontic treatment for malocclusion, surgical enucleation of cysts and treatment of TMJ dysarthrosis may be necessary for management of oral defects.
3. Annual evaluations are important to detect any changes in the spine or sternum. This is particularly important in times of rapid growth, such as adolescence. In some cases, an orthopedic brace or surgery may be recommended to limit damage and disfigurement.
4. In most cases, eyeglasses or contact lenses can correct ocular problems, although surgery may be necessary in some cases.
5. Those with heart problems are encouraged to wear a medical alert bracelet and to go to the emergency room if they experience chest, back, or abdominal pain. Some heart valve problems can be managed with drugs such as beta-blockers, which may help decrease stress on the aorta. In other cases, surgery to replace a valve or repair the aorta may be necessary. Surgery should be performed before the aorta reaches a size that puts it at high risk for tear or rupture.
6. If dural ectasia develops, medication may help minimize any associated pain.

ACHONDROGENESIS (FIG. 10.23)

Marco Fraccardo first described achondrogenesis in 1952.²³ Achondrogenesis is a group of severe disorders that affect cartilage and bone development. These conditions are characterized by a small body, short limbs, and other skeletal abnormalities. As a result of serious health problems, infants with achondrogenesis usually die before birth, are stillborn, or die soon after birth from respiratory failure. Some infants, however, have lived for a short time with intensive medical support.

Researchers have described at least three forms of achondrogenesis, designated as type 1A, type 1B, and type 2. The types are distinguished by their signs and symptoms, inheritance pattern, and genetic cause; however, types 1A and 1B are often hard to tell apart without genetic testing.

Achondrogenesis type 1A, which has also been called the Houston-Harris type, is the least well understood of the three forms. Affected infants have extremely short limbs, a narrow chest, short ribs that fracture easily, and soft skull bones. They also lack normal bone formation (ossification) in the spine and pelvis.

Achondrogenesis type 1B, also known as the Parenti-Fraccaro type, is characterized by extremely short limbs, a narrow chest, and a prominent, rounded abdomen. The fingers and toes are short and the feet may be rotated inward. Affected infants frequently have a soft out-pouching around the belly-button (an umbilical hernia) or near the groin (an inguinal hernia).

Infants with achondrogenesis type 2, which is sometimes called the Langer-Saldino type, have short arms and legs, a



FIGURE 10.23: Achondrogenesis showing short limbs and protuberant abdomen

narrow chest with short ribs, and underdeveloped lungs. This condition is also associated with a lack of ossification in the spine and pelvis. Distinctive facial features include a prominent forehead, a small chin, and, in some cases, an opening in the roof of the mouth (a cleft palate). The abdomen is enlarged, and affected infants often have a condition called hydrops fetalis in which excess fluid builds up in the body before birth.

Achondrogenesis types 1A and 1B are rare genetic disorders; their incidence is unknown. Combined, achondrogenesis type 2 and hypochondrogenesis (a similar skeletal disorder) occur in one in 40,000 to 60,000 newborns.

Mutations in the SLC26A2 and COL2A1 genes cause achondrogenesis types 1B and 2, respectively.²⁴ The genetic cause of achondrogenesis type 1A is unknown.

CLINICAL FEATURES

- Males and females are equally affected.
- Achondrogenesis is detected prenatally or at birth because of typical clinical, radiological, histological, and molecular findings.
- Achondrogenesis type I
 - Growth—Lethal neonatal dwarfism, mean birth weight of 1200 g
 - Craniofacial—Disproportionately large head; soft skull; sloping forehead; convex facial plane; flat nasal bridge, occasionally associated with a deep horizontal groove; small nose, often with anteverted nostrils; long philtrum; retrognathia; increased distance between lower lip and lower edge of chin; double chin appearance (often).
 - Neck—Extremely short.
 - Thorax—Short and barrel-shaped thorax, lung hypoplasia.
 - Heart—Patent ductus arteriosus, atrial septal defect, ventricular septal defect.
 - Abdomen—Protuberant.
 - Limbs—Extremely short (micromelia), much shorter than type II; flipper-like appendages.
- Achondrogenesis type II
 - Growth—Lethal neonatal dwarfism, mean birth weight of 2100 g.
 - Craniofacial—Disproportionately large head, large and prominent forehead, flat facial plane, flat nasal bridge, small nose with severely anteverted nostrils, normal philtrum (often), micrognathia.
 - Neck—Extremely short.
 - Thorax—Short and flared thorax, bell-shaped cage, lung hypoplasia.
 - Abdomen—Protuberant.
 - Limbs—Extremely short (micromelia).

Management

1. Supportive medical care is the only option.
2. No specific treatment for the underlying disorder.

CHONDRODYSPLASIA PUNCTATA

Chondrodysplasia punctata is a clinically and genetically diverse group of rare diseases, first described by Conradi, that share the features of stippled epiphyses and skeletal changes.

TYPES

Rhizomelic Chondrodysplasia Punctata

Rhizomelic chondrodysplasia punctata type 1 (RCDP1) classic type, a peroxisome biogenesis disorder (PBD), is characterized by proximal shortening of the humerus and to a lesser degree the femur (rhizomelia), punctate calcifications in cartilage with epiphyseal and metaphyseal abnormalities (chondrodysplasia punctata, or CDP), coronal clefts of the vertebral bodies, and cataracts that are usually present at birth or appear in the first few months of life. Birth weight, length, and head circumference are often at the lower range of normal; postnatal growth deficiency is profound. Mental deficiency is severe, and the majority of children develop seizures. Most affected children do not survive the first decade of life; a proportion die in the neonatal period. A milder phenotype in which all affected individuals have congenital cataracts and chondrodysplasia is now recognized; some do not have rhizomelia, and some have less severe mental and growth deficiency.²⁵

X-Linked Recessive Chondrodysplasia Punctata

It is caused by defects in arylsulfatase E (ARSE), a vitamin K-dependent enzyme. Affected males have hypoplasia of the distal phalanges without limb shortening or cataracts. The diagnosis is confirmed by molecular genetic testing. Contiguous gene deletions involving *ARSE* result in more complex phenotypes, including ichthyosis and corneal opacities resulting from steroid sulfatase deficiency.

Conradi-Hünemann Syndrome

It is usually lethal in males. It is caused by defects in sterol-8-isomerase, which catalyzes an intermediate step in the conversion of lanosterol to cholesterol. Lyonization in females results in phenotypic variability and asymmetric findings. Cataracts are sectorial and limb shortening is rhizomesomelic and usually asymmetric. Severely affected infants have bilateral findings resembling those of RCDP1. The diagnosis is confirmed by measuring the plasma concentration of sterols, which show accumulation of the precursors 8(9)-cholestenol and 8-dehydrocholesterol.

Autosomal Dominant Chondrodysplasia Punctata

- They are most commonly found.
- It occurs as an autosomal dominant form with the male: female ratio of 3:1.
- Clinically patients with this disorder show flat nasal bridge, high arched palate, hypertelorism, cataract, glaucoma, microphthalmus, ichthyosis, hyperkeratosis, bowing of legs, scoliosis.
- Radiographic findings show shortening of long bones, calcific deposits in infantile cartilaginous skeleton and scoliosis.

Management

1. Management is supportive and limited by the multiple handicaps present at birth and poor outcome.
2. Surveillance includes monitoring of growth and development and regular assessments for seizure control, vision, hearing, contractures, and orthopedic complications.
3. Genetic counseling is also recommended.

PYCNODYSTOSIS

Pycnodysostosis is a condition which is characterized by a hereditary syndrome of short stature, osteoporosis, and skeletal abnormalities.

The name for this disease was coined by the French physicians **Maroteaux and Lamy** in 1962.²⁶ They described the disorder in a report entitled “La pycnodysostose.” (They were not the only discoverers of the disease. **Andren and colleagues** independently described the condition in 1962.) **Maroteaux and Lamy** put “pykno” from the Greek meaning “dense” together with the compound word “dysostosis” meaning abnormal bone formation. The name “pycnodysostosis” was designed to convey the abnormally dense bone that is a hallmark of the disease.

In 1995, the gene for pycnodysostosis was first charted by **Gelb and associates**.²⁷ It was found to travel preferentially with gene markers known to be in chromosome region 1q21. Pycnodysostosis is now clearly recognized as being due to cathepsin K deficiency.

Cathepsin K is an enzyme (a catalyst for a reaction of body metabolism) of the type called a cysteine protease. This protease is important in cells of normal bone (osteoclasts) that are responsible for bone reabsorption. It is thought that osteoclasts in patients with pycnodysostosis are hampered by a lack of cathepsin K and cannot adequately reabsorb that component of bone called the organic matrix. Because of this inadequate resorption, the bones in pycnodysostosis are abnormally dense and brittle.

CLINICAL FEATURES

Pycnodysostosis causes abnormalities of head and face, teeth, collar bones, skin, and nails. The front and back of the head are prominent. Within the open sutures of the skull, there may be many small bones (called wormian bones).

The midface is less full than usual. The nose is prominent.

The jaw can be small. The palate is narrow and grooved. There occurs delayed eruption of deciduous teeth.

The permanent teeth are commonly irregular and teeth may be missing (hypodontia). The collar bones are often underdeveloped and malformed. The skin over the back of the fingers is much wrinkled. The nails are flat and grooved.

Vertebral defects may permit the spine to curve laterally (resulting in scoliosis).

RADIOGRAPHIC FEATURES

Radiographically, generalized osteosclerosis is evident. There is a tendency for bone to fracture.

Skull radiographs reveal “Harlequin appearance” or “Raccoon mask” sign, open fontanelles and cranial sutures, absence of facial sinuses (Fig. 10.24).

Panoramic radiograph may reveal acute mandibular angle and malpositioned teeth (Fig. 10.25)

Management

1. Bone fractures are a big problem for patients with pycnodysostosis. It is important that the disease be diagnosed and the tendency to fractures be recognized so that fractures can be minimized, if not entirely prevented.
2. Replacement treatment with growth hormone was then tested and found effective to increase linear growth of bone.²⁸

MUCOPOLYSACCHARIDOSIS

Mucopolysaccharides (MPS) consist of glycosaminoglycans attached to a link protein with a hyaluronic acid core. Lysosomal enzymes degrade these macromolecules into smaller components. Heparan sulfate, dermatan sulfate, and keratan sulfate are by-products of an incomplete degradation process. The accumulation of these compounds interferes with cell function.

Defective activity of the lysosomal enzymes blocks the degradation process of mucopolysaccharides, leading to abnormal accumulation of heparan sulfate, dermatan sulfate, and keratan sulfate. These degradation by-products are then secreted and detected in the urine. Mucopolysaccharidosis (MPS) can be subclassified according to the type and amount of substance that accumulates, as follows: Hurler syndrome

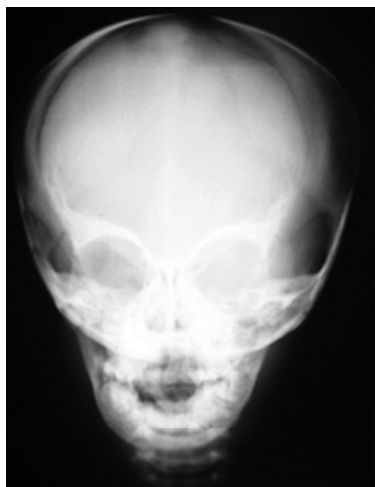


FIGURE 10.24: Postero-anterior skull radiography revealing generalized sclerosis of the skeleton, more pronounced in the periorbital region ("Harlequin appearance" or "Raccoon mask" sign), open fontanelles and cranial sutures, absence of facial sinuses

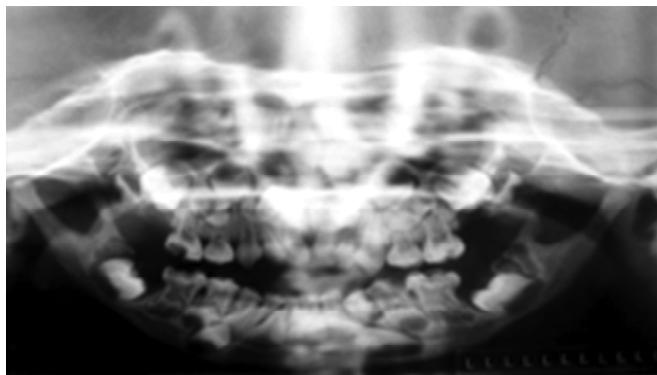


FIGURE 10.25: Panoramic radiography revealing obtuse mandible angle, acute caries and malpositioned teeth

(MPS IH), Hurler-Scheie (MPS I-H/S), Scheie syndrome (MPS IS), Hunter syndrome (MPS II), Sanfilippo syndrome (MPS III), Morquio syndrome (MPS IV), Maroteaux-Lamy syndrome (MPS VI), and Sly syndrome (MPS VII).²⁹⁻³¹

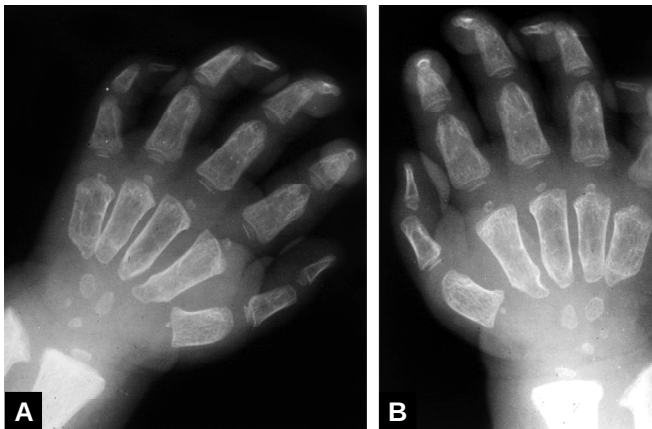
The prevalence of all types of MPS is 1 case in 16,000 to 30,000 births. MPS III accounts for 80 percent of cases. These syndromes are found in persons of all ethnic groups, but prevalence is increased in Israeli Jews and French Canadians.

All mucopolysaccharidoses are inherited as autosomal recessive disorders with the exception of Hunter syndrome (MPS II), which is inherited as sex-linked recessive condition. Thus, all patients with Hunter syndrome are males.

MPS features mostly present in the first few months of life. However, Morquio syndrome usually presents in children aged 2 to 4 years, and MPS IS and MPS VI can present late in childhood.

CLINICAL FEATURES

- **MPS IH (Hurler syndrome):** Infants born with Hurler syndrome appear healthy at birth. Diagnosis is usually made in infants aged 6 to 24 months. Inguinal and umbilical hernias are commonly seen at birth. On physical examination, these patients are observed to have corneal clouding, hepatosplenomegaly, skeletal deformities (dysostosis multiplex), coarse facial features, large tongue, prominent forehead, joint stiffness, and short stature. They also have upper airway obstruction, recurrent ear infections, noisy breathing, and persistent nasal discharge. Other features include hirsutism, hearing loss, hydrocephalus, and mental retardation. Death usually occurs by age 10 years.
- **MPS I-H/S (Hurler-Scheie syndrome):** This is an intermediate form of Hurler syndrome with milder features. Onset is seen in children aged 3 to 8 years. These patients have normal intelligence and micrognathia, which gives them a characteristic facies. Corneal clouding, joint stiffness, and heart disease develop by the early to mid-teens. Patients survive well into the third decade of life.
- **MPS IS (Scheie syndrome):** Onset occurs in patients older than five years. These patients have aortic valve disease, corneal clouding, and joint stiffness with broad short claw hands. They have normal intelligence and stature and a normal life span.
- **MPS II (Hunter syndrome):** Mild and severe forms exist, both of which have the same enzyme deficiency. This form of MPS is characterized by pebbly ivory skin lesions on the back, arms, and thighs. The extent of the skin lesions does not correlate with severity of the disease.
 - **MPS II, severe form:** Onset of disease occurs in children aged 2 to 4 years, with severe progressive somatic and neurologic involvement. Coarse facial features, skeletal deformities (such as claw hand) (Figs 10.26A and B), and joint stiffness are present. These patients also have retinal degeneration with clear cornea and hydrocephalus, mental retardation, and aggressive behavior. Death occurs in patients aged 10 to 15 years.
 - **MPS II, mild form:** These patients have similar features to the severe form but a much slower rate of progression. They have normal intelligence and no hydrocephalus. Hearing impairment and loss of hand function secondary to joint stiffness and deformities are common in the mild form of Hunter. These patients survive into the sixth and seventh decades of life.
- **MPS III (Sanfilippo syndrome):** This appears to be the most common of the MPS disorders. Four subtypes of this disease exist, based on the lysosomal enzyme deficiency (types A, B, C, and D). However, these subtypes are not distinguishable clinically. Onset of the disease usually occurs in children aged 3 to 6 years. These patients have severe central nervous



FIGURES 10.26A and B: Mucopolysaccharidosis showing characteristic skeletal deformity of the hands

system involvement and only minimal somatic involvement. They commonly present with hyperactivity, mental deterioration, and developmental delay. Physical findings include coarse hair, hirsutism, mild hepatosplenomegaly, and enlarged head. Occasionally, mild dysostosis multiplex and joint stiffness are seen. By age 8 to 10 years, these patients are profoundly retarded with severely disturbed social behavior (e.g. uncontrollable hyperactivity, destructive physical aggression). These patients usually survive into the second or third decade of life.

- **MPS IV (Morquio syndrome):** Deficiencies of two different enzymes leading to a severe form (MPS IV A) and a mild form (MPS IV B) are recognized. Orthopedic involvement is the primary finding in these patients, with preservation of intelligence and varying degrees of skeletal involvement. Spondyloepiphyseal dysplasia is the hallmark of this disease. Physical findings include genu valgum, short stature, spinal curvature, odontoid hypoplasia, and ligamentous laxity. Atlantoaxial instability is common in Morquio syndrome and can lead to severe myelopathy, paralysis, and death. Patients with the severe form do not survive beyond the third or fourth decade of life. Patients with the mild form have much slower progression of skeletal dysplasia and a normal life span.
- **MPS VI (Maroteaux-Lamy syndrome):** Onset occurs in patients aged 1 to 3 years. Mild, intermediate, and severe types have been identified, all with the same enzyme deficiency. Features are very similar to Hurler syndrome, including corneal clouding, coarse facies, joint stiffness, skeletal deformities, and heart valvular disease. Intelligence, however, is normal. These patients may survive into the third decade of life. Most die from cardiopulmonary complications.
- **MPS VII (Sly syndrome):** This is a very rare condition. Mild and severe forms have been identified. The severe form of

MPS VII can be detected in the neonatal period associated with hydrops fetalis and hepatosplenomegaly, with death occurring within the first few months of life. Patients with the mild form survive into adolescence. The phenotype is similar to that of Hurler syndrome. Physical findings include corneal clouding, coarse facies, macrocephaly, metatarsus adductus, prominent sternum, pelvic hypoplasia, hepatosplenomegaly, and hernias.

Management

1. Specific treatment or cure is limited for MPS. Management has been limited to supportive care and experimental treatment modalities.
2. Laronidase (Aldurazyme) is a polymorphic variant of the human enzyme alpha-L-iduronidase produced by recombinant DNA technology. It is indicated to treat MPS type I (Hurler and Hurler-Scheie forms). It increases catabolism of glycosaminoglycans (GAGs), which accumulate with MPS I. Laronidase therapy has shown to improve walking capacity and pulmonary function.
3. Idursulfase (Elaprase) is a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. It hydrolyzes 2-sulfate esters of terminal iduronate sulfate residues from the GAGs dermatan sulfate and heparan sulfate in the lysosomes of various cell types. It is used to replace insufficient levels of the lysosomal enzyme iduronate-2-sulfatase in MPS II.³²
4. Bone marrow transplantation (BMT) has been successful in the treatment of MPS conditions, especially Hurler syndrome.³³
5. Surgical management for specific conditions like hydrocephalus, cardiovascular disease, obstructive airway disease, orthopedic conditions is recommended.

RICKETS

Rickets is a disease of growing bone that is unique to children and adolescents. It is caused by a failure of osteoid to calcify in a growing person. Failure of osteoid to calcify in adults is called osteomalacia. Vitamin D deficiency rickets occurs when the metabolites of vitamin D are deficient. Less commonly, a dietary deficiency of calcium or phosphorus may also produce rickets. Vitamin D-3 (cholecalciferol) is formed in the skin from a derivative of cholesterol under the stimulus of ultraviolet-B light.

Natural nutritional sources of vitamin D are limited primarily to fatty, ocean-going fish. In the United States, dairy milk is fortified with vitamin D (400 IU/L). Human milk contains little vitamin D, generally less than 20 to 40 IU/L. Therefore, infants who are breastfed are at risk for rickets, especially those who receive no oral supplementation and those who have darkly pigmented skin, which blocks penetration of ultraviolet light.

In the vitamin D deficiency state, hypocalcemia develops, which stimulates excess parathyroid hormone, which stimulates renal phosphorus loss, further reducing deposition of calcium in the bone. Excess parathyroid hormone also produces changes in the bone similar to those occurring in hyperparathyroidism. Early in the course of rickets, the calcium concentration in the serum decreases. After the parathyroid response, the calcium concentration usually returns to the reference range, though phosphorus levels remain low. Alkaline phosphatase, which is produced by overactive osteoblast cells, leaks to the extracellular fluids so that its concentration rises to anywhere from moderate elevation to very high levels.

Intestinal malabsorption of fat and diseases of the liver or kidney may produce the clinical and secondary biochemical picture of nutritional rickets. Anticonvulsant drugs (e.g. phenobarbital, phenytoin) accelerate metabolism of calcidiol, which may lead to insufficiency and rickets, particularly in children who are kept indoors in institutions.

Calcium and vitamin D intakes are low in infants who are fed vegan diets, particularly lactovegans, and monitoring of their vitamin D status is essential.

Recent studies have noted that disorders of increased fibroblast growth factor 23 (FGF-23) functions are associated with rickets.³⁴

CLINICAL AND RADIOGRAPHIC FEATURES

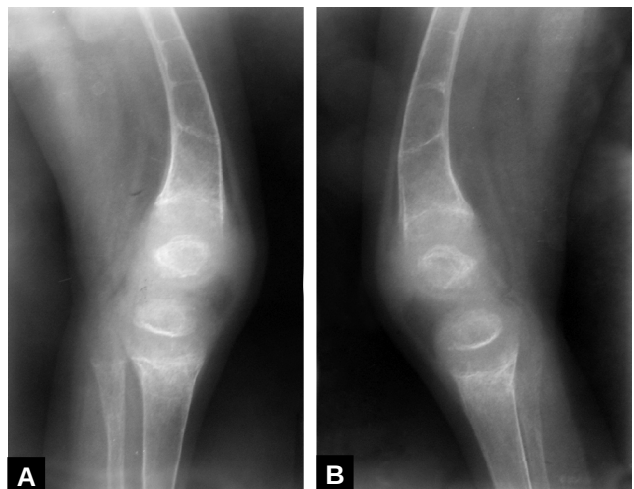
- No sexual predilection is noted.
- It is observed only in growing children, although the effects may be observed later in life.
- Generalized muscular hypotonia of an unknown mechanism is observed in most patients with clinical (as opposed to biochemical and radiographic) signs of rickets.
- Craniotabes manifests early in infants with vitamin D deficiency, although this feature may be normal in infants, especially for those born prematurely.
- If rickets occurs at a later age, thickening of the skull develops. This produces frontal bossing and delays the closure of the anterior fontanelle. In the long bones, laying down of uncalcified osteoid at the metaphyses leads to spreading of those areas, producing knobby deformity, which is visualized on radiography as cupping and flaring of the metaphyses.
- Weight bearing produces deformities such as bowlegs and knock-knees (Figs 10.27 to 10.30).
- In the chest, knobby deformities results in the rachitic rosary along the costochondral junctions. The weakened ribs pulled by muscles also produce flaring over the diaphragm, which is known as Harrison groove. The sternum may be pulled into a pigeon-breast deformity.
- In more severe instances in children older than two years, vertebral softening leads to kyphoscoliosis. The ends of the



FIGURE 10.27: Rickets showing bowed legs in a child



FIGURE 10.28: Rickets showing bowed hands in a child



FIGURES 10.29A and B: Rickets showing bowing of bones of the legs leading to a typical knock knee appearance in a child



FIGURE 10.30: Rickets showing deformity of bones of the forearms seen in rickets

long bones demonstrate that same knobby thickening. At the ankle, palpation of the tibial malleolus gives the impression of a double epiphysis (Marfan sign). Because the softened long bones may bend, they may fracture one side of the cortex (i.e. greenstick fracture). Panoramic radiograph may reveal poorly defined lamina dura around the teeth (Fig. 10.31).

HISTOPATHOLOGIC FEATURES

Lesional areas when observed show uncalcified cartilage matrix covering the shaft of long bones separated by the capillaries. Osteoid is formed on the cartilage but it does not calcify.

Management

1. Treatment for rickets may be gradually administered over several months or in a single-day dose of 15,000 mcg (600,000 U) of vitamin D. If the gradual method is chosen, 125-250 mcg (5000-10,000 U) is given daily for 2-3 months until healing is well established and the alkaline phosphatase concentration is approaching the reference range.
2. If the vitamin D dose is administered in a single day, it is usually divided into four or six oral doses. An intramuscular injection is also available. Vitamin D is well stored in the body and is gradually released over many weeks. Because both calcitriol and calcidiol have short half-lives, they are unsuitable; they would bypass the natural physiologic controls of vitamin D synthesis.
3. If severe deformities have occurred, orthopedic correction may be required after healing. Most of the deformities correct with growth.
4. Human milk contains little vitamin D and contains too little phosphorus for babies who weigh less than 1500 g.



FIGURE 10.31: Rickets showing poorly defined lamina dura around the teeth

5. Infants weighing less than 1500 g need special supplementation (i.e. vitamin D, calcium, phosphorus) if breast milk is their primary dietary source.
6. Recommending a vitamin D supplement from the first week of life for susceptible infants who are breastfed is safe and effective and, therefore, should be considered.

HYPERPARATHYROIDISM

There are four parathyroid glands located below the thyroids. These glands produce parathormone and maintain plasma ionized calcium levels. Any deviation from the normal activity of secretion from these glands either leads to hypo or hypersecretion from these glands which manifests in the form of symptoms of hypo or hyperparathyroidism respectively. It may be primary or secondary.

Primary hyperparathyroidism is a disease which occurs as a result of excessive secretion of parathyroid hormones. It may occur due to adenoma of the glands, hyperplasia of parathyroid tissue or due to carcinoma of the gland. Secondary hyperparathyroidism occurs when parathormone is secreted continuously as a result of low levels of serum parathormone due to some kind of renal disease. Primary hyperparathyroidism occurs during childhood and is therefore considered here.

CLINICAL FEATURES

- It occurs most commonly in women.
 - Incidence of occurrence is most common in middle aged persons but may also be seen in children.
 - Bone and joint pains, and pathologic fractures are most common findings.
 - Sometimes there occurs giant cell tumor in the bones.
- Schour and Massler**, 1943,³⁵ reported that malocclusion due to drifting of teeth may be the first sign of this disease.

- There is elevated level of serum calcium above the normal level of 9 to 12 mg/dl and serum parathormone.

RADIOGRAPHIC FEATURES

The lesion appears radiolucent and has been described as 'ground glass' appearance when it occurs in jaws. Sometimes there is partial loss of lamina dura around the teeth.

HISTOPATHOLOGIC FEATURES

- Lesional area does not show any pathognomonic changes for this lesion but shows osteoclastic resorption of the bony trabeculae.
- Osteoblastic rimming is seen around the osteoid.
- Fibrosis is seen replacing resorbed bone.
- Presence of hemosiderin pigments and giant cells is evident.

Management

Surgical excision of the parathyroid tissue is performed to reduce the levels of parathormone to normal.

HYPOPARATHYROIDISM

Hypoparathyroidism results from defective synthesis or secretion of Parathyroid hormone (PTH), end-organ resistance, or inappropriate regulations that result from the activated or antibody-stimulated Calcium-sensing receptor (CaSR). These defects can be inherited or acquired. PTH secretion by the parathyroid glands (prime regulators of serum calcium concentration) maintains serum calcium within a strict range. Biochemical hallmarks of hypoparathyroidism include hypocalcemia and hyperphosphatemia. Severe hypocalcemia presents with seizures, stridor and tetany.

Mature PTH is an 84-amino acid protein. Production and secretion of PTH are regulated by a G protein-coupled calcium-sensing receptor. Unlike other protein hormones, its production and secretion are stimulated by decreased intracellular calcium concentrations, which reflect serum calcium concentrations. PTH exerts its action through the PTH receptor, which is another member of the G protein-linked receptor family.

The net effects of PTH activity are an increase in serum calcium and a decrease in serum phosphate. PTH acts directly on bone to stimulate bone resorption and cause calcium and phosphate release. PTH acts directly on the kidney to decrease calcium clearance and to inhibit phosphate reabsorption. By stimulating renal 1-alpha-hydroxylase activity, PTH increases serum concentrations of 1,25-dihydroxyvitamin D, the active form of vitamin D and, thus, indirectly stimulates calcium and phosphate absorption by the gut through the actions of vitamin D. The phosphaturic effect of PTH offsets the increases of serum phosphate driven by increased bone resorption and GI absorption.

Hypoparathyroidism results in loss of the direct and indirect effects of PTH on bone, the kidney, and the gut. Calcium and phosphate release from bone is impaired, calcium absorption from the gut is limited, calciuria develops despite hypocalcemia, and retention of phosphate from the urine causes increased plasma phosphate levels.

Hypoparathyroidism may be transient, genetically inherited, or acquired.

Genetically inherited forms arise from defects of parathyroid gland development, defects in the parathyroid hormone (PTH) gene, defects in the calcium-sensing receptor gene, defects in PTH action, defects in the autoimmune regulator gene, and genetic syndromes.

Acquired hypoparathyroidism may be due to an autoimmune process or may occur after neck irradiation or surgery.

Transient hypoparathyroidism occurs during the neonatal period. Preterm infants are at increased risk, and as many as 50 percent of very low birth weight infants may have a deficient surge in PTH that results in hypocalcemia.

- Hypocalcemia is noted in 10 to 20 percent of infants of diabetic mothers. These infants may be born prematurely, which is a risk factor for insufficient PTH response. They may have hypomagnesemia from maternal magnesuria complicating glucosuria. Low serum magnesium can impair PTH release and action.
- DiGeorge syndrome (i.e. hypoparathyroidism, T-cell abnormalities, cardiac anomalies) is associated with abnormal development of the third and fourth pharyngeal pouches from which the parathyroids derive embryologically and represents an example of a defect in parathyroid gland development. DiGeorge syndrome and velocardio-facial syndrome are variants of the chromosome arm 22q11 microdeletion syndrome.
- Hypocalcemia associated with a 22q11 microdeletion may be transiently present in infancy but recur later in life, particularly during periods of stress.
- Familial cases of hypoparathyroidism due to mutations of the PTH gene located on chromosome arm 11p15 have been identified. These mutations have been both dominantly and recessively inherited.

CLINICAL FEATURES

- Hypoparathyroidism is equally prevalent in males and females.
- Age of onset depends on the etiology of hypoparathyroidism. Newborns may present with hypoparathyroidism; however, it can manifest at almost any age.
- Hyper-reflexia due to hypocalcemia is common.
- Trousseau sign is a carpopedal spasm that occurs after a blood pressure cuff around the arm is inflated to the systolic blood pressure for several minutes.

- Chvostek sign (i.e. twitching of facial muscles with tapping on the facial nerve in front of the ear) is a manifestation of neuromuscular irritability. Chvostek sign is present in 25 percent of healthy adults and in even higher rates in children. Thus, its presence or absence should be documented prior to thyroidectomy.
- Nasal speech can occur from a cleft palate or velopharyngeal insufficiency.
- Bulbous nasal tip, micrognathia, ear anomalies, and short philtrum are typical facial features but may not be evident in nonwhite children.
- A heart murmur may signify a conotruncal heart defect.
- Short stature may be a feature of the genetic syndrome, but in some cases, it is due to hypopituitarism.

Management

1. Symptomatic hypocalcemia (e.g. seizure, tetany, laryngospasm) in patients with hypoparathyroidism requires intravenous calcium and continuous monitoring for cardiac arrhythmias.
2. Oral calcium and vitamin D should be initiated as soon as possible (e.g., when the patient is tolerating oral feeds).
3. Once serum calcium concentrations are in a safe range (>7.5 mg/dL), intravenous calcium can be stopped. However, rebound hypocalcemia can occur and requires that a patient be monitored for therapeutic success on oral agents for at least 24 hours after intravenous calcium is withdrawn.
4. The active form of vitamin D, 1,25-dihydroxyvitamin D, is preferred in the treatment of hypoparathyroidism because both the parathyroid hormone (PTH) deficiency/resistance and the hyperphosphatemia impair the activation of 25-hydroxyvitamin D by 1- α -hydroxylase.
5. No special diet is required, but adequate calcium and vitamin D intake is recommended.
6. Calcium and vitamin D are the mainstays of treatment for hypoparathyroidism and pseudohypoparathyroidism (PHP). To relieve immediate severe symptoms of hypocalcemia, an intravenous bolus of 9-15 mg elemental calcium/kg (1 g calcium gluconate = 90 mg elemental calcium = 4.5 mEq elemental calcium) is administered over 10-30 min. Then, either intermittent boluses or a continuous IV infusion is initiated (≤ 60 mg elemental calcium/kg/d). Oral calcium is initiated for a total of 100 mg elemental calcium/kg/d divided 4 times daily. Once serum calcium concentrations range from 8 to 9 mg/dL, the calcium dose is weaned to the minimum dose necessary to maintain a low-normal serum calcium concentration.
7. Numerous calcium preparations are available. An intravenous dose quickly but transiently corrects the serum calcium concentration and relieves hypo-

calcemic symptoms. Severe hypocalcemia can be treated with a continuous calcium infusion; a transition to the oral form can be made when the serum calcium concentration is within a safe range. Tailoring of calcium dosing to each patient's needs is essential. In fact, once adequate amounts of active vitamin D are present, some patients can absorb all the calcium they need through the diet and oral calcium preparations can be discontinued.

CRANIOSYNOSTOSIS SYNDROMES

Craniosynostosis consists of premature fusion of one or more cranial sutures, often resulting in an abnormal head shape. It may result from a primary defect of ossification (primary craniosynostosis) or, more commonly, from a failure of brain growth (secondary craniosynostosis). Simple craniosynostosis is a term used when only 1 suture fuses prematurely. Complex or compound craniosynostosis is used to describe premature fusion of multiple sutures. When children with craniosynostosis, usually complex, also display other body deformities, this is termed syndromic craniosynostosis.

When one or more sutures fuse prematurely, skull growth can be restricted perpendicular to the suture. If multiple sutures fuse while the brain is still increasing in size, intracranial pressure can increase.

- Scaphocephaly – Early fusion of the sagittal suture
- Anterior plagiocephaly – Early fusion of 1 coronal suture
- Brachycephaly – Early bilateral coronal suture fusion
- Posterior plagiocephaly – Early closure of 1 lambdoid suture
- Trigonocephaly – Early fusion of the metopic suture.

More frequent than the primary type, secondary craniosynostosis can result from early fusion of sutures due to primary failure of brain growth. Since brain growth drives the bony plates apart at the sutures, a primary lack of brain growth allows premature fusion of all the sutures.

Intracranial pressure is usually normal, and surgery is seldom needed. Typically, failure of brain growth results in microcephaly. Premature suture closure does not compromise brain growth and does not require surgery to open sutures.

Intrauterine space constraints may play a role in the premature fusion of sutures in the fetal skull. This has been demonstrated in coronal craniosynostosis. Other secondary causes of craniosynostosis include systemic disorders that affect bone metabolism such as rickets and hypercalcemia.

- Multiple theories have been proposed for the etiology of primary craniosynostosis, but the most widely accepted is a primary defect in the mesenchymal layer ossification in the cranial bones.
- Secondary craniosynostosis typically results from systemic disorders such as the following:

- Endocrine–Hyperthyroidism, hypophosphatemia, vitamin D deficiency, renal osteodystrophy, hypercalcemia, and rickets
- Hematologic disorders that cause bone marrow hyperplasia (e.g. sickle cell disease, thalassemia)
- Inadequate brain growth, including microcephaly and its causes and shunted hydrocephalus.
- The syndromic causes appear to result from genetic mutations responsible for fibroblast growth factor receptors two and three. A gene locus for single suture craniosynostosis has not been identified.
- Other important factors to consider
 - Differentiating plagiocephaly that results from positional molding (which does not require surgery and is seen frequently) from lambdoid suture fusion is extremely important.
 - The presence of multiple suture fusions strongly suggests a craniofacial syndrome, which frequently requires the diagnostic expertise of a pediatric geneticist.

CLINICAL FEATURES

Craniosynostosis is equally distributed in both boys and girls.

- Neonatal period: Craniosynostosis is evident at birth when associated with other craniofacial abnormalities.
- Infancy (0–18 mo): Secondary or primary craniosynostosis becomes evident as the child grows.
- Microcephaly usually suggests a secondary craniosynostosis.
- Scaphocephaly
 - Premature fusion of the sagittal suture is the most common craniosynostosis, constituting more than half of all cases. It occurs frequently in premature infants.
 - The head typically is elongated in the anterior-posterior diameter and shortened in the biparietal diameter. Ridging of the sagittal suture is palpable.
- Anterior plagiocephaly – Premature fusion of one coronal suture.
- Brachycephaly
 - Premature fusion of both coronal sutures results in increased biparietal diameter. This anomaly is often syndromic. The skull is shorter in the anterior-posterior diameter.
 - Because the coronal suture develops in conjunction with the sutures at the base of the skull, unilateral or bilateral mid and upper face hypoplasia may occur. Orbits may be elliptical (i.e. Harlequin features), and the supraorbital ridge may not be formed well.
 - Consider these features when planning surgery for brachycephaly.

- Posterior plagiocephaly
 - The two predominant causes of posterior plagiocephaly are craniosynostosis of the lambdoid suture (<2%) or positional molding (vast majority).
 - Since the American Academy of Pediatrics recommended that infants sleep on their backs to reduce sudden infant death syndrome (SIDS) incidence, positional molding has been seen with increased frequency.
 - Torticollis is frequently associated with positional molding.
 - Viewed from above, the head shape in positional molding resembles a parallelogram, whereas that in lambdoid craniosynostosis is trapezoid shaped.
 - In positional molding, ear position is more anterior on the side of flattening; in lambdoid synostosis, ear position is more posterior.
 - Frontal bossing is observed ipsilateral to the flattening in positional molding and contralateral in lambdoid synostosis.
- Trigonocephaly
 - Premature fusion of the metopic suture frequently results in pointed forehead (i.e. triangular shaped head). The abnormality is usually mild and requires no surgical intervention. Surgery is performed if the abnormality is persistent and severe.
 - Oxycephaly (i.e. turricephaly) is fusion of all skull sutures and the sutures at the base of the skull.
- Craniosynostosis sometimes is associated with sporadic craniofacial syndromes such as Crouzon, Apert, Chotzen, Pfeiffer, or Carpenter syndromes. In this context, facial features, typically craniofacial abnormalities, suture ridging, and early closure of fontanelles, suggest the diagnosis.
- Kleeblattschädel (i.e. cloverleaf skull) results from fusion of all sutures except the metopic and squamosal sutures, giving the head a cloverleaf appearance.
- Intracranial pressure may be elevated in primary multiple suture craniosynostosis, such as cloverleaf skull and the syndromic synostoses. Signs include sun-setting eyes, papilledema, vomiting, and lethargy.

Management

1. Currently, surgery is usually cosmetic for infants with fusion of 1 to 2 sutures that result in a misshapen head. For infants with microcephaly (i.e. secondary craniosynostosis), surgery usually is not required.
2. Surgery typically is indicated for increased intracranial pressure or for cosmetic reasons.
3. Consideration for cosmetic surgery is dependent on the age of presentation and on which sutures have

fused prematurely. Cosmetic surgery is performed in infants aged 3 to 6 months.

4. Infants with a defined syndrome causing craniosynostosis should be evaluated early for surgery. Results are best when surgery is performed in infants younger than six months. Patients with associated facial deformities may need a staged surgical approach.
5. No surgery is indicated for posterior plagiocephaly secondary to positional molding. The vast majority of infants improve with repositioning maneuvers and physical therapy for torticollis.

CRANIOFACIAL DYSOSTOSIS – CROUZON SYNDROME (FIG. 10.32)

- In 1912, Crouzon described the hereditary syndrome of craniofacial dysostosis in a mother and son. He described the triad of calvarial deformities, facial anomalies, and exophthalmos.³⁶
- Crouzon syndrome is an autosomal dominant disorder with complete penetrance and variable expressivity. It is characterized by premature closure of calvarial and cranial base sutures as well as those of the orbit and maxillary complex (craniosynostosis).
- Other clinical features include hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, hypoplastic maxilla, and relative mandibular prognathism. Unlike some other forms of autosomal dominant craniosynostosis, no digital abnormalities are present.

Crouzon syndrome is caused by mutations in the fibroblast growth factor receptor-2 (FGFR2) gene but exhibits locus heterogeneity with causal mutations in FGFR2 (Crouzon syndrome) and FGFR3 (Crouzon syndrome with acanthosis nigricans) in different affected individuals.



FIGURE 10.32: Crouzon syndrome in a patient showing hypertelorism

- Premature synostosis of the coronal, the sagittal, and, occasionally, the lambdoid sutures begins in the first year of life and is completed by the second or third year. The order and rate of suture fusion determine the degree of deformity and disability. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure. Compensatory growth occurs at the remaining open sutures to allow continued brain growth. However, multiple sutural synostoses frequently extend to premature fusion of the skull base sutures, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia, and occasional upper airway obstruction.
- The phenotypic spectrum of the FGFR3 P250R mutation, called Muenke craniosynostosis or FGFR3-associated coronal synostosis, is so widely variable that patients with this specific mutation had been previously diagnosed as having Crouzon syndrome, Pfeiffer syndrome, Saethre-Chotzen syndrome, Jackson-Weiss syndrome, and nonsyndromic craniosynostosis.³⁷
- A newly identified mutation in the tyrosine kinase I domain of the FGFR2 gene (1576A>G, encoding the missense substitution Lys526Glu) is associated with variable expressivity of Crouzon syndrome, including clinical nonpenetrance.

CLINICAL FEATURES

- Crouzon syndrome has no known sex predilection.
- The condition is detected in the newborn or infant period because of dysmorphic features.
- Craniosynostosis: Craniosynostosis commonly begins during the first year of life and usually completes by the second or third year. Coronal and sagittal sutures are most commonly involved, resulting in acrocephaly, brachycephaly, turriccephaly, oxycephaly, flat occiput, and high prominent forehead with or without frontal bossing. Ridging of the skull is usually palpable. Cloverleaf skull is rare (only 7%) and occurs in the most severely affected individuals.
- Flattened sphenoid bone
- Shallow orbits
- Hydrocephalus (progressive in 30%)
- Midface (maxillary) hypoplasia may be present.
- Exophthalmos (proptosis) secondary to shallow orbits resulting in frequent exposure conjunctivitis or keratitis
- Ocular hypertelorism
- Divergent strabismus
- Rare occurrence of nystagmus, iris coloboma, aniridia, anisocoria, microcornea, megalocornea, cataract, ectopia lentis, blue sclera, glaucoma, luxation of the eye globes, papilledema, and optic atrophy from raised intracranial pressure leading to blindness.

- Beaked appearance
- Compressed nasal passage
- Choanal atresia or stenosis
- Deviated nasal septum
- Mandibular prognathism
- Overcrowding of upper teeth, malocclusions, and V-shaped maxillary dental arch
- Narrow, high, or cleft palate and bifid uvula
- Occasional oligodontia, macrodontia, peg-shaped, and widely spaced teeth
- Narrow or absent ear canals
- Deformed middle ears
- Cervical fusion (18%), C2 to C3, C3 to C4, and C5 to C6
- Block fusions involving multiple vertebrae
- Subluxation of the radial heads
- Ankylosis of the elbows
- Approximately 5 percent of patients have acanthosis nigricans, which is detectable after infancy. The hallmark of these lesions is a darkened thickened skin with accentuated markings and a velvety feel.
- Approximately 73 percent of patients have chronic tonsillar herniation (47 percent have progressive hydrocephalus).
- Syringomyelia may be present.
- Postnatal subtype of Crouzon syndrome (in patients at risk, such as family members of patients with Crouzon syndrome, or those with some degree of exorbitism at birth) from birth to at least age three years.
- Development of digital impressions and/or ossification of sutures starting at the occipital region of the skull.
- Development of a prominent bregma.
- Development of “spontaneous” intracranial hypertension.
- Progressive characteristic crouzonoid features such as progressive exorbitism.

Management

1. Early detection of eye problems to reduce amblyopia by correction of refractory errors and timely treatment of strabismus and patching is indicated. Optic atrophy remains an important cause of visual impairment before decompressive craniectomy.³⁸
2. To relieve airway obstruction, a nasal continuous positive airway pressure device may be needed.
3. Close otologic and audiologic follow-up is indicated to detect sensorineural hearing loss. Management of speech may be necessary.
4. Surgical treatment varies according to the variable expressivity of the disease and usually begins during a child's first year with fronto-orbital advancement with cranial decompression. Subsequent development of midfacial hypoplasia needs correction. Procedures for this purpose include the Le Fort III osteotomy or its segmental variants, monobloc frontofacial advancement, or bipartition osteotomy.

5. Early craniectomy with frontal bone advancement is most often indicated to prevent or treat increased intracranial pressure because newborns with Crouzon syndrome develop multiple suture synostoses and fused synchondroses.
6. Fronto-orbital and midfacial advancements help in the cosmetic reconstruction of facial dysmorphisms.
7. A new technique, craniofacial disjunction, followed by gradual bone distraction (Ilizarov procedure) has been reported to produce complete correction of exophthalmos and improvement in the functional and aesthetic aspects of the middle third of the face without the need for bone graft in patients aged 6 to 11 years.

MANDIBULOFACIAL DYSOSTOSIS – TREACHER COLLINS FRANCESCHETTI SYNDROME (FIG. 10.33)

Mandibulofacial dysostosis, also known as Treacher Collins syndrome was named after the eminent British ophthalmologist Edward Treacher Collins (1862-1932), who described the essential features of this syndrome in a paper in 1900.³⁹ However, some features of this syndrome were probably first described by *Thomson and Toynbee*^{40,41} in 1846 to 1847 and later by Berry (1889),⁴² who is usually given credit for its discovery. It is an inherited developmental disorder with a prevalence estimated to ranges between one in 40,000 to one in 70,000 of live births. Growth of craniofacial structures derived from the first and second pharyngeal arch, groove, and pouch is diminished symmetrically and bilaterally.

Inheritance of Treacher Collins syndrome is autosomal dominant, with complete penetrance and variable expressivity. Nonpenetrance is rare. Approximately 60 percent of cases represent fresh mutations.



FIGURE 10.33: Treacher Collins syndrome showing downward displacement of mouth and recession of chin

Treacher Collins syndrome is caused by mutations in the *TCOF1* gene. *TCOF1* was mapped to chromosome bands 5q31.3-33.3. The *TCOF1* gene codes for the treacle protein, which may be involved in nucleolar trafficking and is required for normal craniofacial development. Single mutations in the gene result in the premature termination of the protein product.⁴³

CLINICAL FEATURES

- Males and females are equally affected.
- In the vast majority of cases, Treacher Collins syndrome is clearly diagnosed at birth.
- The face of an individual with Treacher Collins syndrome is characteristic. Abnormalities are usually present bilaterally and symmetrically. The nose has a normal size; however, it appears large because of hypoplastic supraorbital rims and hypoplastic zygomas. The palpebral fissures are downward-sloping, the pinnae are malformed with widely varying severity, and the chin recedes with a large, down-turned mouth.
- A cleft palate is found in one third of patients with Treacher Collins syndrome, and congenital palatopharyngeal incompetence (foreshortened, immobile, or absent soft palate; submucous cleft palate) is found in an additional one-third of patients. The parotid glands are missing or hypoplastic. Pharyngeal hypoplasia is a constant finding.

RADIOGRAPHIC FEATURES

The malar bones, zygomatic process of frontal bone, lateral pterygoid plates, paranasal sinuses, and mandibular condyles are hypoplastic. The mastoids are not pneumatized. The lateral margins of the orbits may be defective, and the orbits are hyperteloritic. The cranial base is progressively kyphotic. The calvaria are essentially normal. The mandibular angle is more obtuse than normal and the ramus is deficient. The coronoid and condyloid processes are flat or aplastic. There is hypoplasia and a repositioned tongue. There occur difficulties with swallowing and feeding (caused by musculoskeletal underdevelopment and a cleft palate).

Management

1. In patients with severe manifestations in which airway inadequacy is the prominent feature after birth, a tracheostomy is performed. To relieve airway obstruction, a nasal continuous positive airway pressure device may be needed.
2. In patients with severe swallowing difficulty, introduce feeding by gavage or even through a gastrostomy tube to ensure adequate caloric intake and hydration.
3. Fit hearing aids shortly after birth if the patient has substantial conductive hearing loss. Hearing aids are important for the development of the infant's communication skills and for the normal bonding process within the family.

4. Operative repair of Treacher Collins syndrome is based upon the anatomic deformity and timing of correction is done according to physiologic need and development.
5. A new management technique has been performed in selected cases. Distraction osteogenesis, an orthopedic method of lengthening bone, has been used to lengthen the neonatal mandible. The infant is intubated at birth, and, within a few days, a cut is made on both sides of the jaw and distraction hardware is placed. The jaw is stretched at 1 to 2 mm/d, and extubation is usually performed when 10 mm of lengthening is achieved.
6. For more minor obstructions that can be corrected with positioning, a tongue-lip adhesion is considered. Surgical adhesion is performed between the tongue, lip, and anterior mandible. This pulls the tongue forward, correcting the base of tongue obstruction, and pulls the tongue out of the nasopharynx in the presence of cleft palate.
7. The lateral coloboma of the lower eyelid has traditionally been corrected with a skin-muscle flap from the upper lid or brow. This adds vertical height to the lateral lid, correcting the notch and down-turned lateral palpebral fissure.
8. Macrostomia, if present, can be repaired at the same time with Z-plasty or straight-line skin repair; however, restoration of continuity in the oral musculature is important, as it restores the function of the oral sphincter and limits scar contracture.
9. Cleft palate, present in one third of cases, is repaired at approximately age 10 to 12 months but can be delayed if airway concerns exist. Extra time before cleft palate repair allows for some mandibular growth to occur prior to the surgical narrowing of the airway with repair of the palate.
10. Microtia is addressed at age 5 to 7 years, which is when the external ear is approximately 80-90 percent of adult size and rib cartilage is of sufficient volume to use as graft material. The ear is constructed in 3 stages; the first stage is the most involved. Autologous costochondral grafts are usually harvested from the fifth, sixth, and seventh rib.
11. Osteotomies and bone grafts address the long midface, short mandible, and lateral facial clefts.
12. The Le Fort osteotomy II is performed to derotate the middle face with the nasofrontal junction as the fulcrum. The maxilla and nasal bones are disjoined from the cranium to shorten the anterior midface while lengthening the posterior facial height.
13. A compensatory mandibular osteotomy is performed to both vertically and horizontally lengthen the jaw and equilibrate the dental occlusion. Bone grafts fill in the congenital defects at the lateral orbital rim, zygoma, and malar prominence. This stage of

reconstruction is the most invasive and physically taxing on the patient. Additional procedures such as rhinoplasty and genioplasty (chin advancement) can be performed after the major osteotomies.

PIERRE ROBBIN SYNDROME (FIG. 10.34)

Lannelongue and Menard first described Pierre Robin syndrome in 1891 in a report on two patients with micrognathia, cleft palate, and retroglossoptosis.⁴⁴ In 1923, Pierre Robin published the case of an infant with the complete syndrome. Until 1974, the triad was known as Pierre Robin syndrome; however, the term syndrome is now reserved for those errors of morphogenesis with the simultaneous presence of multiple anomalies caused by a single etiology. The term sequence has been introduced to include any condition that includes a series of anomalies caused by a cascade of events initiated by a single malformation.

Three pathophysiological theories exist to explain the occurrence of Pierre Robin sequence.

1. The mechanical theory: This theory is the most accepted. The initial event, mandibular hypoplasia, occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios could play a role in the etiology since the lack of amniotic fluid could cause deformation of the chin and subsequent impaction of the tongue between the palatal shelves.
2. The neurological maturation theory: A delay in neurological maturation has been noted on electromyography of the tongue musculature, the pharyngeal pillars, and the palate,

as has a delay in hypoglossal nerve conduction. The spontaneous correction of the majority of cases with age supports this theory.

3. The rhombencephalic dysneurulation theory: In this theory, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

CLINICAL FEATURES

- Micrognathia is reported in the majority of cases (91.7%). It is characterized by retraction of the inferior dental arch 10 to 12 mm behind the superior arch. The mandible has a small body, obtuse gonial angle, and a posteriorly located condyle. The growth of the mandible catches up during the first year; however, mandibular hypoplasia resolves and the child attains a normal profile by approximately age 5 to 6 years.
- Glossoptosis is noted in 70 to 85 percent of reported cases. Macroglossia and ankyloglossia are relatively rare findings, noted in 10 to 15 percent of reported cases.
- The combination of micrognathia and glossoptosis may cause severe respiratory and feeding difficulty in the newborn. Obstructive sleep apnea may also occur.
- The most common otic anomaly is otitis media, occurring 80 percent of the time, followed by auricular anomalies in 75 percent of cases. Hearing loss, mostly conductive, occurs in 60 percent of patients, while external auditory canal atresia occurs in only 5 percent of patients.
- Nasal deformities are infrequent and consist mostly of anomalies of the nasal root. Dental and philtral malformations occur in one-third of cases.
- Speech defects occur frequently in patients with Pierre Robin sequence. Velopharyngeal insufficiency is usually more pronounced in these patients than in those with isolated cleft palate.
- Cardiovascular findings such as benign murmurs, pulmonary stenosis, patent ductus arteriosus, patent foramen ovale, atrial septal defect, and pulmonary hypertension have all been documented.
- Anomalies involving the musculoskeletal system include syndactyly, dysplastic phalanges, polydactyly, clinodactyly, hyperextensible joints, and oligodactyly in the upper limbs. In the lower extremities, foot anomalies (clubfeet, metatarsus adductus), femoral malformations (coxa varus or valgus, short femur), hip anomalies (flexure contractures, congenital dislocation), anomalies of the knee (genu valgus, synchondrosis), and tibial abnormalities have been reported. Vertebral column deformities include scoliosis, kyphosis, lordosis, vertebral dysplasia, sacral agenesis, and coccygeal sinus.
- Central nervous system (CNS) defects such as language delay, epilepsy, neurodevelopmental delay, hypotonia, and hydrocephalus may occur.



FIGURE 10.34: Pierre Robin syndrome showing severe mandibular retrognathism

- Genitourinary defects may include undescended testes (25%), hydronephrosis (15%), and hydrocele (10%).
- Associated syndromes and conditions include Stickler syndrome, trisomy 11q syndrome, trisomy 18 syndrome, velocardiofacial (Shprintzen) syndrome, deletion 4q syndrome, rheumatoid arthropathy, hypochondroplasia, Möbius syndrome, and CHARGE association.

Management

1. Children with severe micrognathia may have significant respiratory obstruction at birth, requiring a nasopharyngeal airway or intubation.
2. For most newborns, the earliest physical problem involves feeding. The cleft hampers the generation of enough negative pressure to nurse. The milk or formula has to be delivered through a bottle with a nipple that has a large hole cut into the top to make the delivery effortless.
3. The cleft palate team includes pediatricians, otolaryngologists, plastic surgeons, pedodontists, orthodontists, nurses, speech therapists, audiologists, and social workers. The most common procedure is the single-stage palate (hard and soft) closure, performed when the child is aged 6 to 18 months.
4. Although many different surgical procedures have been described, tracheostomy remains the most widely used technique. Other surgical procedures, such as subperiosteal release of the floor of the mouth, and different types of glossopexy, such as the Routledge procedure or other forms of tongue-lip adhesions, can be used. Any glossopexy should be released before significant dentition develops (age 9–12 mo). Mandibular lengthening by gradual distraction may be used for severe mandibular hypoplasia that causes obstructive apnea.⁴⁵
5. As the therapy of choice to correct the conductive hearing loss and prevent middle ear complications, tympanostomy tubes are usually inserted when the palatoplasty is performed.

APERT SYNDROME

- Apert syndrome is named after the French physician who described the syndrome acrocephalosyndactylia in 1906.⁴⁶
- Apert syndrome is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet.
- During early infancy, the coronal suture area is prematurely closed. A bony condensation line beginning at the cranial base and extending upward with a characteristic posterior convexity represents this occurrence. Anterior and posterior fontanelles are widely patent. The midline of the calvaria

has a gaping defect, extending from the glabellar area to the posterior fontanelle via the metopic suture area, anterior fontanelle, and sagittal suture area. The skull with a gaping midline defect appears to permit adequate accommodation of the growing brain. The lambdoidal sutures appear normal in all cases.

- During the first 2 to 4 years of life, the midline defect is obliterated by coalescence of the enlarging bony islands without evidence of any proper formation of sutures. An extreme short squama and orbital part of the frontal bone together with the posterior convexity of the coronal bone condensation line suggest that growth inhibition in the sphenofrontal and coronal suture area has its onset very early in fetal life.
- Unique fibroblast growth factor receptor 2 (FGFR2) mutations lead to an increase in the number of precursor cells that enter the osteogenic pathway. Ultimately, this leads to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development. The order and rate of suture fusion determine the degree of deformity and disability. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure. Compensatory growth occurs at the remaining open sutures to allow continued brain growth; however, complex, multiple sutural synostosis frequently extends to premature fusion of the sutures at the base of the skull, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia, and occasional upper airway obstruction (Fig. 10.39).

CLINICAL FEATURES

- Apert syndrome has no sex predilection.
- Apert syndrome is detected in the newborn period due to craniosynostosis and associated findings of syndactyly in the hands and feet.
- Craniostenosis is present. Coronal sutures most commonly are involved, resulting in acrocephaly, brachycephaly, turribrachycephaly, flat occiput, and high prominent forehead.
- Large late-closing fontanelles are observed.
- A gaping midline defect is present.
- A rare cloverleaf skull anomaly is present in approximately 4 percent of infants.
- Common facial features during infancy include horizontal grooves above the supraorbital ridges that disappear with age, a break in the continuity of the eyebrows, and a trapezoid-shaped mouth at rest.
- A flattened, often asymmetric face is observed.
- Maxillary hypoplasia with retruded midface is present.

- Patients have apparent low-set ears with occasional conductive hearing loss and congenital fixation of stapedial footplate.
- Eyes exhibit down-slanting palpebral fissures, hypertelorism, shallow orbits, proptosis, exophthalmos, strabismus, (Fig. 10.35) amblyopia, optic atrophy, and, rarely, luxation of the eye globes, keratoconus, ectopic lentis, congenital glaucoma, lack of pigment in the fundi with occasional papilledema, and preventable visual loss or blindness.
- The nose has a markedly depressed nasal bridge. It is short and wide with a bulbous tip, parrot-beak appearance, and choanal stenosis or atresia (Fig. 10.36).
- The mouth area has a prominent mandible, down-turned corners, high arched palate, bifid uvula, and cleft palate.
- Orthodontic problems include crowded upper teeth, malocclusion, delayed dentition, ectopic eruption, shovel-shaped incisors, supernumerary teeth, V-shaped maxillary dental arch, bulging alveolar ridges, dentitio tarda, some impaction, partial eruption, idiopathic root resorption, transposition or other aberrations in the position of the tooth germs, and severe crowding (Figs 10.37 and 10.38).
- The upper limbs are more severely affected than lower limbs.
- Syndactyly involves the hands and feet with partial-to-complete fusion of the digits, often involving second, third, and fourth digits. These are often termed mitten hands and sock feet. In severe cases, all digits are fused, with the palm deeply concave and cup-shaped and the sole supinated (Figs 10.39 and 10.40).
- Hitchhiker posture or radial deviation of short or broad thumbs results from abnormal proximal phalanx.
- Common CNS malformations include megalencephaly, agenesis of the corpus callosum, malformed limbic structures, variable ventriculomegaly, encephalocele, gyral abnormalities, hypoplastic cerebral white matter, pyramidal tract abnormalities, and heterotopic gray matter. Progressive hydrocephalus is uncommon.
- Papilledema and optic atrophy with loss of vision may be present in cases of subtle increased intracranial pressure.
- Congenital cervical spinal fusion (68%), especially C5-C6 (Figs 10.41A and B)
- Aplasia or ankylosis of shoulder, elbow, and hip joints
- Tracheal cartilage anomalies
- Rhizomelia
- Hyperhidrosis (common)
- Synonychia
- Brittle nails
- Acneiform lesions (frequent after adolescence)
- Interruption of the eyebrows
- Hypopigmentation

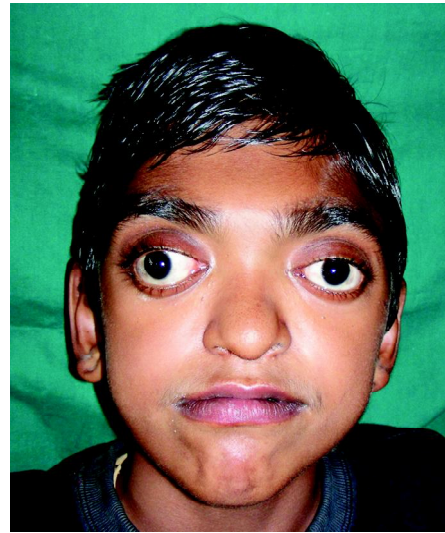
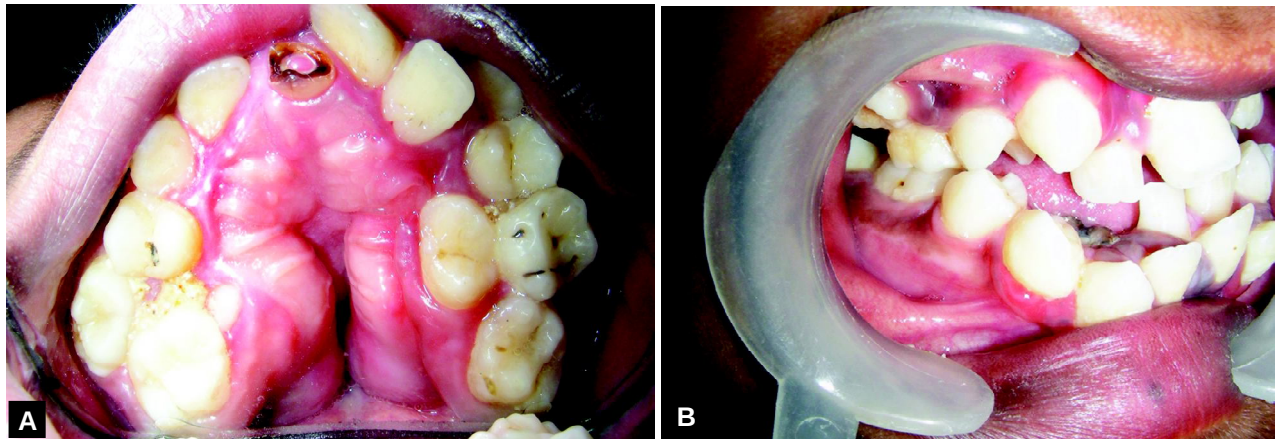


FIGURE 10.35: Extraoral photograph of Apert syndrome showing strabismus and hypertelorism

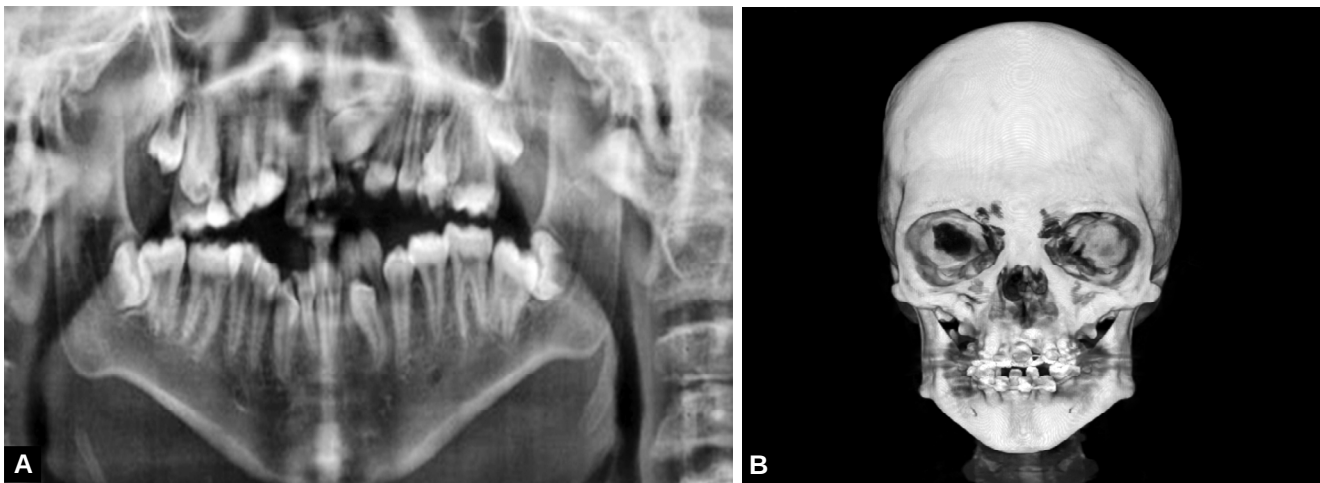


FIGURE 10.36: Extraoral photograph of Apert syndrome showing midface hypoplasia with a relative mandibular prognathism and depressed nasal bridge

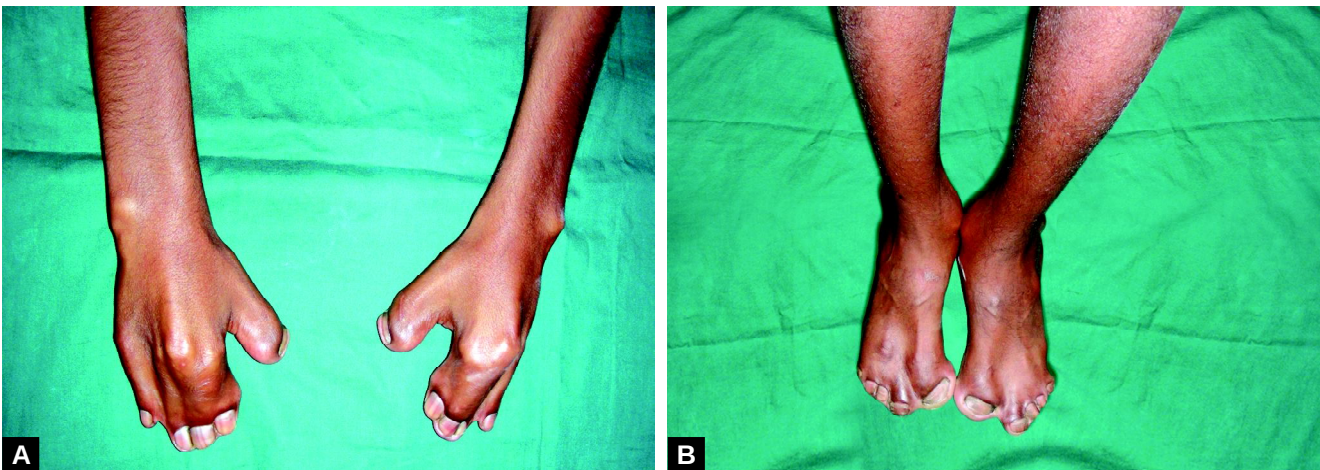
- Hyperkeratosis in the plantar surface
- Paronychial infections (more common in feet than hands and in patients who are institutionalized)
- Excessive skin wrinkling of forehead
- Skin dimples at knuckles, shoulders, and elbows
- Atrial septal defect
- Patent ductus arteriosus
- Ventricular septal defect
- Pulmonary stenosis
- Overriding aorta
- Coarctation of aorta



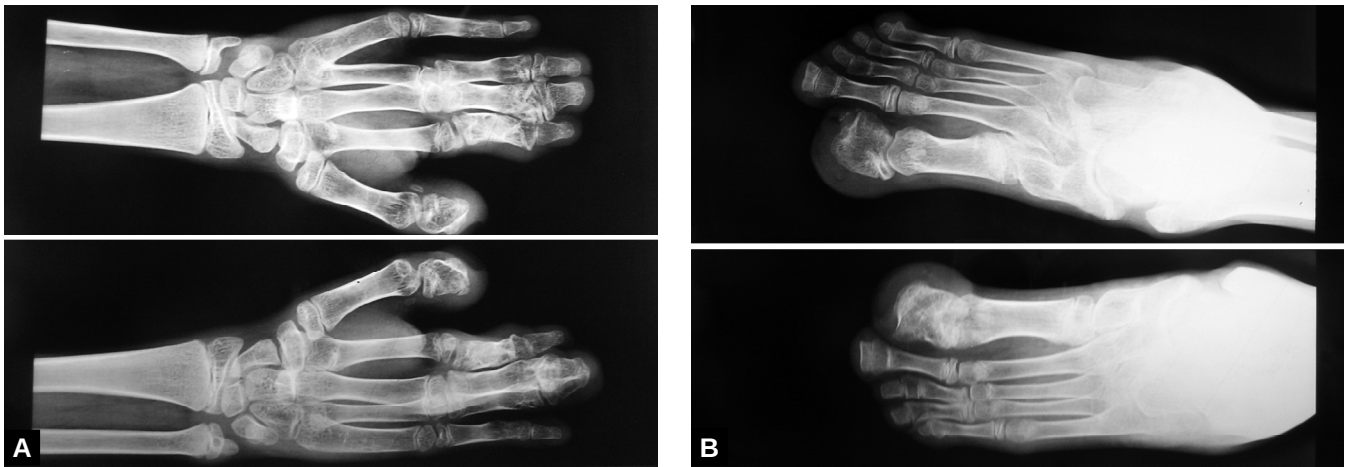
FIGURES 10.37A and B: Intraoral photograph of Apert syndrome showing high arched palate with pseudocleft, ectopic teeth eruption, crowding of teeth and malformed molars, macrodontia of premolars, crowding of teeth and Class III malocclusion



FIGURES 10.38A and B: Panoramic radiograph of Apert syndrome showing over retained teeth, impacted teeth, macrodontia of premolars and prominent gonial angle with vertical ramus of the mandible and three-dimensional computerized tomography showing craniostenosis



FIGURES 10.39A and B: Both hands of Apert syndrome showing syndactyly of 2nd, 3rd and 4th digits and both feet showing syndactyly of all digits



FIGURES 10.40A and B: Hands X-ray (left) of Apert syndrome showing syndactyly of 2nd, 3rd and 4th digits and feet X-ray (right) showing syndactyly of all the toes



FIGURES 10.41A and B: Skull radiograph on left of Apert syndrome revealing brachycephaly with characteristic beaten metal appearance and cervical spine X-ray on right showing congenital fusion of neural arches of C3-C4 and C5-C6-C7

- Dextrocardia
- Tetralogy of Fallot
- Endocardial fibroelastosis
- Polycystic kidneys
- Duplication of renal pelvis
- Hydronephrosis
- Stenosis of bladder neck
- Bicornuate uterus
- Vaginal atresia
- Protuberant labia majora
- Clitoromegaly
- Cryptorchidism
- Pyloric stenosis
- Esophageal atresia and tracheoesophageal fistula
- Ectopic or imperforate anus

- Partial biliary atresia with agenesis of gall bladder
- Anomalous tracheal cartilage
- Tracheoesophageal fistula
- Pulmonary aplasia
- Absent right middle lobe of lung
- Absent interlobular lung fissures.

Management

1. Protection of the cornea.
2. Instill lubricating bland ointments in the eyes at bedtime to protect corneas from desiccation.
3. Artificial teardrops during the day.
4. Remove excessive nasal secretions.
5. Treat upper airway infection.
6. Humidification with added oxygen.

7. Judicious use of topic nasal decongestants.
8. Sleep apnea
9. Polysomnography (a sleep recording of multiple physiologic variables), currently the most reliable method for determining the presence of sleep apnea.
10. Continuous positive pressure.
11. Chronic middle ear effusion associated with bilateral conductive hearing deficit - Antimicrobial therapy.
12. Psychological and social challenges confronted by individuals with Apert syndrome.
13. Emotional adjustment.
14. Cranial surgery.
15. Facial cosmetic reconstruction.
16. A new technique of craniofacial disjunction, followed by gradual bone distraction (Ilizarov procedure), has been reported to produce complete correction of exophthalmos and improvement in the functional and aesthetic aspects of the middle third of the face without the need for bone graft in patients aged 6-11 years.
17. Surgical separation of digits (mitten-glove syndactyly) provides relatively little functional improvement. Shunting procedure reduces intracranial pressure.
18. For orthodontic treatment, most patients require 2-jaw surgery (bilateral sagittal split osteotomy with mandibular setback and distraction in the maxilla).
19. Alternatively, orthodontic treatment may comprise of alignment and levelling of the arches using 0.014 CuNiTi followed by 0.016 NiTi and other suitable management of local malpositioning of teeth (Fig. 10.42).

Custom made toothbrushes may be provided to improve the manual dexterity of the patient (Fig. 10.43).

THANATOPHORIC DYSPLASIA

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia that is lethal in the neonatal period. The term thanatophoric derives from the Greek word thanatophorus, which means “death bringing”. Characteristics of thanatophoric dysplasia include severe shortening of the limbs, a narrow thorax, macrocephaly, and a normal trunk length. Thanatophoric dysplasia is divided into two clinically defined subtypes. Thanatophoric dysplasia type 1 (TD1), the most common subtype, is characterized by a normal-shaped skull and curved long bones (shaped like a telephone receiver); the femurs are most affected. Thanatophoric dysplasia type 2 (TD2) is associated with a cloverleaf-shaped skull and straight femurs. Some clinical overlap exists between the two subtypes. Autosomal dominant mutations in the fibroblast growth factor receptor three gene (FGFR3), which has been mapped to chromosome band 4p16.3, results in both subtypes. The vast majority of cases are due to *de novo* mutations.

The following mutations that affect distinct domains of FGFR3 cause the thanatophoric dysplasia subtypes:

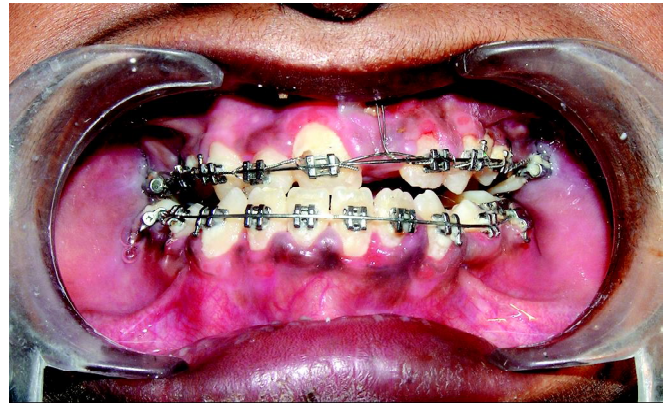


FIGURE 10.42: Frontal view of the arches during orthodontic treatment

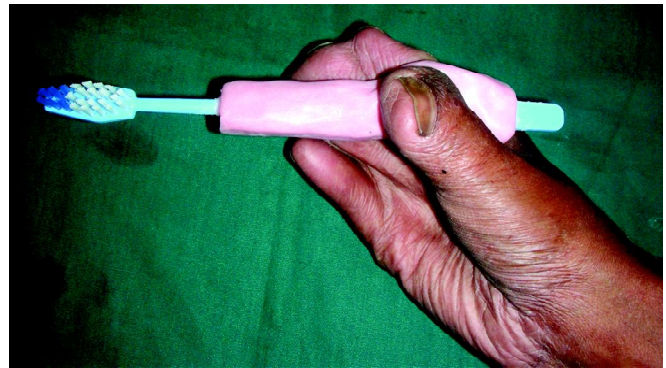


FIGURE 10.43: Patient holding the custom made toothbrush for improvement of manual dexterity

- TD1: Amino acid substitutions in the extracellular domain of FGFR3 have resulted in TD1. The most common mutation in TD1 is arg248cys, which is present in approximately 50 percent of patients.
- TD2: In patients with TD2, lys650blu is the only reported gene mutation.

Patients with TD2 have a single recurrent mutation (A-to-G) in the tyrosine kinase domain of FGFR3, but patients with TD1 have different mutations that affect either the extracellular or intracellular domains of FGFR3. The most common TD1 mutation is a C-to-T transition, which results in a change of arginine to cysteine in the extracellular domain of FGFR3.

CLINICAL FEATURES

- Males and females are equally affected.
- Thanatophoric dysplasia is lethal in neonates; however, long-term survival has been reported.
- Severe growth deficiency with an average length of 40 cm at term.
- A macrocephalic head with a frontal bossing, a flattened nasal bridge, and proptotic eyes.

- In TD2, a cloverleaf-shaped skull due to premature closure of the cranial sutures.
- Narrow thorax with small ribs.
- Micromelic limbs with brachydactyly.
- Protuberant abdomen.
- Hydrocephalus and other cerebral parenchymal abnormalities.

Management

1. Inpatient care is necessary. Intubation may be performed as aggressive treatment for respiratory distress.
2. If aggressive treatment is deferred, palliative treatment consists of keeping the infant warm, comfortable, and nourished.

ACHONDROPLASIA

Achondroplasia, a nonlethal form of chondrodysplasia, is the most common form of short-limb dwarfism. It is inherited as a Mendelian autosomal dominant trait with complete penetrance. Approximately 80 percent of cases are due to new or *de novo* dominant mutations with a mutation rate estimated to be 0.000014 per gamete per generation. Salient phenotypic features include disproportionate short stature, megalencephaly, a prominent forehead (frontal bossing), midface hypoplasia, rhizomelic shortening of the arms and legs, a normal trunk length, prominent lumbar lordosis, genu varum, and a trident hand configuration (Fig. 10.44).



FIGURE 10.44: Achondroplasia showing rhizomelic shortening of the arms and legs

Achondroplasia is caused by mutations in the fibroblast growth factor receptor-3 (FGFR3) gene. This gene has been mapped to chromosome 4, band p16.3 (4p16.3).

CLINICAL FEATURES

- It is usually seen in children.
- Males and females are equally affected.
- Hypotonia in infancy and early childhood.
- Delayed motor milestones.
- Normal intelligence with possible minor deficit in visual-spatial tasks.
- Large calvarial bones in contrast to the small cranial base and facial bones.
- True megalencephaly (large head) with frontal bossing.
- Midface hypoplasia.
- Dental malocclusion and crowding.
- Disproportionate short stature.
- Normal trunk length that appears long and narrow, small thoracic cage.
- Rhizomelic shortening of the proximal limbs with redundant skin folds.
- Brachydactyly and trident hand configuration: A marked separation between the ring and middle fingers giving the hand a 3-pronged appearance.
- Thoracolumbar gibbus (lumbar kyphosis) in infancy, which is replaced by an exaggerated lumbar lordosis once ambulation begins.
- Hyperextensibility of most joints, especially the knees.
- Limited elbow extension and rotation.
- Genu varum (bow legs).

RADIOGRAPHIC FEATURES

- Contracted skull base.
- Progressive interpedicular narrowing in the lumbar spine region.
- Short pedicles which can cause spinal stenosis.
- Short femoral neck and metaphyseal flaring.
- Dysplastic ilium, narrow sacroiliac groove, flat-roofed acetabula.

Management

1. Closely monitor growth in patients with achondroplasia.
2. Perform careful neurologic examinations.
3. Manage frequent middle ear infections and address any concerns for hearing loss.
4. Orthodontic treatment is recommended for dental malocclusion and crowding.
5. Control weight to prevent obesity and associated comorbidities.

6. Therapy is performed using growth hormone (GH) to foster linear growth.
7. Anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are useful to alleviate pain and inflammation for patients with degenerative joint disease.
8. Leg-lengthening procedures using distraction osteogenesis have been performed successfully. Successful height increase is reported to be 12 to 14 inches. Better outcomes are reported with the use of the Orthofix Garches lengthening device along with tenotomy of the Achilles tendon and syndesmosis, which provide the fewest complications with healing indices similar to those of other operative protocols. Another procedure associated with fewer complications in children and adolescents younger than 14 years is tibia, rather than femur, lengthening.
9. In children with signs of craniomedullary compression, surgical treatment to release the compression can improve neurologic, cognitive, and respiratory functions. Indications for the possible need for suboccipital decompression include lower limb hyperreflexia or clonus on examination, central hypopnea demonstrated by polysomnography, and foramen magnum measurements lower than the mean.
10. Lumbar laminectomy can be performed for spinal stenosis, which is a condition that usually manifests in early adulthood.

ROBINOW SYNDROME

Robinow syndrome is an extremely rare genetic disorder characterized by short-limbed dwarfism, abnormalities in the head, face, and external genitalia, as well as vertebral segmentation. The disorder was first described in 1969 by human geneticist **Meinhard Robinow**, along with physicians Frederic N Silverman and Hugo D Smith, in the American Journal of Diseases of Children.⁴⁷

Two forms of the disorder exist, dominant and recessive, of which the former is more common. Patients with the dominant version often suffer moderately from the aforementioned symptoms. Recessive cases, on the other hand, are usually more physically marked, and individuals may exhibit more skeletal abnormalities.

Genetic studies have linked the autosomal recessive form of the disorder to the ROR2 gene on position nine of the long arm of chromosome nine. The gene is responsible for aspects of bone and cartilage growth. This same gene is involved in causing autosomal dominant brachydactyly.

CLINICAL FEATURES

- **Robinow** noted the resemblance of affected patients' faces to that of a fetus, using the term "fetal facies" to describe the appearance of a small face and widely spaced eyes.
- Other craniofacial and oral features include hypertelorism (wide apart eyes), short upturned nose, broad nasal bridge (wide, flat nose), anteverted nares (upturned nose), triangular mouth (bottom corners face downward), frontal bossing (boxlike forehead), long/short philtrum (upper lip), micrognathia (small chin), wide palpebral fissures (wide eye openings), down slanting palpebral fissures (slanted eyes), ear abnormality (small and lower set), facial nevus (birthmark on face), normal intelligence, dental abnormalities/malaligned teeth (crowded, crooked, missing teeth), gingival hyperplasia (thick gums), abnormal uvula (heart shaped), cleft lip/palate (non-midline) and shortened tongue/some with midline indentation.
- Though the eyes do not protrude, abnormalities in the lower eyelid may give that impression. Surgery may be necessary if the eyes cannot close fully. In addition, the ears may be set low on the head or have a deformed pinna.
- Patients suffer from dwarfism, short lower arms, small feet, and small hands. Fingers and toes may also be abnormally short and laterally or medially bent. The thumb may be displaced and some patients, notably in Turkey, experience ectrodactyly. All patients often suffer from vertebral segmentation abnormalities. Those with the dominant variant have, at most, a single butterfly vertebra. Those with the recessive form, however, may suffer from hemivertebrae, vertebral fusion, and rib anomalies. Some cases resemble Jarcho-Levin syndrome or spondylocostal dysostosis.
- Genital defects characteristically seen in males include a micropenis with a normally developed scrotum and testes. Sometimes, testicles may be undescended, or the patient may suffer from hypospadias. Female genital defects may include a reduced size clitoris and underdeveloped labia minora. Infrequently, the labia majora may also be underdeveloped. Some research has shown that females may experience vaginal atresia or hematocolpos.
- The autosomal recessive form of the disorder tends to be much more severe. Examples of differences are summarized in the Table 10.4.⁴⁸

TABLE 10.4: Difference between autosomal dominant and recessive Robinow syndrome

Characteristic	Autosomal dominant	Autosomal recessive
Stature	More than 2 SD shorter	Short or normal
Arms	Very short	Slightly short
Elbow	Radial head dislocation	No dislocation
Upper lip	Very broad	Tented
Mortality rate	Normal	10%

Management

There is no specific treatment for Robinow syndrome, but for ROR2-related Robinow syndrome, specific treatment modalities are as follows:

- Orofacial assessment to determine the need for plastic surgery.
- Dental assessment for misaligned, crowded teeth.
- Radiographic documentation of the forearm shortening and hand anomalies.
- Micropenis assessment for reconstructive surgery.
- Corrective surgery may be necessary for the eyes if they cannot close fully.
- Several corrective surgeries are usually required for the limb and spine defects and facial abnormalities.
- In individuals with growth hormone deficiency, response to growth hormone therapy is good and near normal height can be attained.
- Injection of human chorionic gonadotropin to improve penile length and testicular volume is recommended. Hormone therapy should be monitored by a pediatric endocrinologist.
- Orthodontic treatment is usually required.

HYPEROSTOSIS CORTICALIS GENERALISATA

First documented in 1955 by Van Buchem, the skeletal condition that carries his name was categorized as hyperostosis corticalis generalisata.⁴⁹ Van Buchem disease is an autosomal recessive bone dysplasia linked to a genetic locus on chromosome 17q12–21.⁵⁰

CLINICAL FEATURES

This disease is characterized by a symmetrically increased thickness of bones, most frequently found as an enlarged jawbone, but also an enlargement of the skull, ribs, diaphysis of long bones, as well as tubular bones of hands and feet, resulting in increased cortical bone density.

The clinical consequences of increased thickness of the skull include facial nerve palsy causing hearing loss, visual problems, neurological pain, and, very rarely, blindness as a consequence of optic atrophy.

The most common radiological features are massive hyperostosis of the calvarium and mandible, resulting in increased weight of skull and sclerosis of the diaphyses of the long bones, clavicles, ribs, and pelvis with disruption of bone contours resulting in a very rough bone surface.⁵¹

Bone anomalies are symmetric, appearing in the first decade of life and becoming more prominent among the oldest patients, suggesting progression of disease with aging.

Bony changes in Van Buchem disease are consistent with increased bone formation, but clear evidence of increased bone formation has not been obtained.

Management

There is no specific treatment for this disorder.

CHONDROECTODERMAL DYSPLASIA

- In 1940, *Ellis and van Creveld* (Ellis and van Creveld, 1940) formally described the syndrome that would bear their names, although they termed it chondroectodermal dysplasia.⁵²
- Pathophysiology of this syndrome is unknown; however, recent identification of the *EVC* gene should lead to a better understanding.⁵³

CLINICAL FEATURES

- Frequency of Ellis-van Creveld syndrome is equal in males and females.
- In patients with Ellis-van Creveld syndrome, physical findings, such as disproportionate extremities, small stature, polydactyly, cardiac defects, and minor dysmorphic features, are seen at birth.
- A clinical tetrad of Ellis-van Creveld syndrome consists of chondrodystrophy, polydactyly, ectodermal dysplasia, and cardiac anomalies.
- Chondrodystrophy (the most common feature affecting the tubular bones):
 - Disproportionate dwarfism (small stature of prenatal onset; average adult height, 109–155 cm).
 - Progressive distal limb shortening, symmetrically affecting the forearms and lower legs.
- Polydactyly (Fig. 10.45):
 - Bilateral and postaxial.
 - Polydactyly, observed in the hands in most cases but in the feet in 10% of cases.



FIGURE 10.45: Ellis-van Creveld syndrome showing polydactyly

- Hidrotic ectodermal dysplasia (observed in as many as 93% of cases):
 - Nails are hypoplastic, dystrophic, and friable. Nails can be completely absent in some cases.
 - Tooth involvement may include neonatal teeth, partial anodontia, small teeth, and delayed eruption. Enamel hypoplasia may result in abnormally shaped teeth with frequent malocclusion.
 - Hair may occasionally be sparse.
- Congenital cardiac anomalies:
 - Heart defects occur in 50 to 60% of patients; the most common anomaly is a common atrium (40%).
 - Other cardiac anomalies include atrioventricular canal, ventricular septal defect, atrial septal defect, and patent ductus arteriosus.
 - The cardiac anomaly is the major cause of shortened life expectancy.
- Other anomalies may also be present.
- Musculoskeletal anomalies include low-set shoulders, a narrow thorax frequently leading to respiratory difficulties, knock knees, lumbar lordosis, broad hands and feet, and sausage-shaped fingers.
- Oral lesions include the following:
 - A fusion of the anterior portion of the upper lip to the maxillary gingival margin, resulting in an absence of mucobuccal fold and the upper lip to present a slight V-notch in the middle.
 - Short upper lip, bound by frenula to alveolar ridge (lip tie).
 - Often serrated lower alveolar ridge.
 - Teeth may be prematurely erupted at birth or exfoliate prematurely.
- Occasional genitourinary anomalies include hypospadias, epispadias, hypoplastic penis, cryptorchidism, vulvar atresia, focal renal tubular dilation in medullary region, nephrocalcinosis, renal agenesis, and megaureters.
- Occasionally, CNS anomalies or mental retardation are present.
- Clinical manifestations in heterozygous carriers:
 - Polydactyly has been reported in relatives of four unrelated Ellis-van Creveld syndrome families.
 - A father of a child with Ellis-van Creveld syndrome who had finger and teeth abnormalities has been reported, as have several other reports of symptomatic heterozygous manifestations.

HISTOPATHOLOGIC FEATURES

Histopathologic examination of fetuses with Ellis-van Creveld syndrome revealed that the cartilage of long bones showed chondrocyte disorganization in the physeal growth zone.

Variable chondrocyte disorganization was seen in the central physeal growth zone of the vertebrae.

Management

1. The management of Ellis-van Creveld (EVC) syndrome is multidisciplinary.
2. Care for respiratory distress, recurrent respiratory infections, and cardiac failure is supportive.
3. Dental care in childhood includes the following:
 - Neonatal teeth should be removed because they may impair feeding.
 - Prevention of caries includes dietary counseling, plaque control, and oral hygiene instruction.
 - Crown or composite build-ups for microdonts may be indicated.
 - Partial dentures can maintain space and improve mastication, esthetics, and speech due to congenitally missing teeth.
 - For dental care during adulthood, implants and prosthetic rehabilitation are required to replace congenitally missing teeth.
4. In cases of short stature considered as a result of chondrodysplasia of the legs, a possible treatment with growth hormone is considered ineffective.
5. Orthopedic procedures correct polydactyly and other orthopedic malformations.
6. Cardiac surgery may be needed to correct cardiac anomalies.
7. Thoracic expansion has been attempted in some patients.
8. Dental care is usually necessary.
9. Urologic surgery is required if epispadias, cryptorchidism, or both are present.
10. Perioperative morbidity may result from difficulties with airway management and pulmonary abnormalities.

TRICHODENTO-OSSEOUS SYNDROME

A rare genetic disorder characterized by kinky hair, tooth enamel and bone abnormalities. There are two different subtypes with type I being distinguished from type II by the presence of a small head and increased density in the long bones.

CLINICAL FEATURES

- Kinky hair
- Small teeth
- Widely spaced teeth (Fig. 10.46)
- Pitted teeth (Fig. 10.46)
- Poor tooth enamel
- Increased tooth pulp chamber size (Fig. 10.47)
- Frontal bossing
- Long head



FIGURE 10.46: Trichodento-Osseous syndrome showing pitted and widely spaced teeth



FIGURE 10.47: Trichodento-Osseous syndrome showing large pulp chambers

- Squarish jaw
- Increased bone density
- Delayed bone age
- Round face
- Brittle nails
- Superficial nail peeling
- Dense long bones
- Thin nails
- Premature nails
- Thickened top portion of skull
- Small head
- Poorly pneumatized mastoids
- Obliterated frontal sinuses
- Undertubulated clavicles.

RADIOGRAPHIC FEATURES

Dental radiographs of this disorder show large pulp chambers and sometimes numerous unerupted teeth are evident.

Management

1. There is no specific treatment for this disorder.
2. Treatment is aimed at cosmetic reconstruction.



FIGURE 10.48: Down syndrome showing mongoloid facie

DOWN SYNDROME (FIG. 10.48)

- In 1866, **Down** described clinical characteristics of the syndrome that now bears his name.⁵⁴
- In 1959, Lejeune and Jacobs et al independently determined that trisomy 21 is the cause.⁵⁵
- Down syndrome is by far the most common and best known chromosomal disorder in humans and the most common cause of intellectual disability.
- Mental retardation, dysmorphic facial features, and other distinctive phenotypic traits characterize the syndrome.
- The extra chromosome 21 affects almost every organ system and results in a wide spectrum of phenotypic consequences. These include life-threatening complications, clinically significant alteration of life course (e.g. mental retardation), and dysmorphic physical features. Down syndrome decreases prenatal viability and increases prenatal and postnatal morbidity. Affected children have delays in physical growth, maturation, bone development, and dental eruption.
- The extra copy of the proximal part of 21q22.3 appears to result in the typical physical phenotype: mental retardation, characteristic facial features, hand anomalies, and congenital heart defects. Molecular analysis reveals that the 21q22.1-q22.3 region, or Down syndrome critical region (DSCR), appears to contain the gene or genes responsible for the congenital heart disease observed in Down syndrome. A new gene, *DSCR1*, identified in region 21q22.1-q22.2, is highly expressed in the brain and the heart and is a candidate for involvement in the pathogenesis of Down syndrome, particularly, in mental retardation and/or cardiac defects.⁵⁶
- Abnormal physiologic functioning affects thyroid metabolism and intestinal malabsorption. Frequent infections

are presumably due to impaired immune responses, and the incidence of autoimmunity, including hypothyroidism and rare Hashimoto thyroiditis, is increased.

- Patients with Down syndrome have decreased buffering of physiologic reactions, resulting in hypersensitivity to pilocarpine and abnormal responses on sensory-evoked electroencephalographic tracings. Children with leukemic Down syndrome also have hyperreactivity to methotrexate. Decreased buffering of metabolic processes results in a predisposition to hyperuricemia and increased insulin resistance. Diabetes mellitus develops in many affected patients. Premature senescence causes cataracts and Alzheimer disease. Leukemoid reactions of infancy and an increased risk of acute leukemia indicate bone-marrow dysfunction.
- Children with Down syndrome are predisposed to developing leukemia, particularly transient myeloproliferative disorder and acute megakaryocytic leukemia. Nearly all children with Down syndrome who develop these types of leukemia have mutations in the hematopoietic transcription factor gene, *GATA1*. Leukemia in children with Down syndrome requires at least three cooperating events: trisomy 21, a *GATA1* mutation, and a third undefined genetic alteration.

CLINICAL FEATURES

- The male-to-female ratio is increased (approximately 1.15:1) in newborns with Down syndrome. This effect is restricted to free trisomy 21.
- Down syndrome can be diagnosed prenatally with amniocentesis, percutaneous umbilical blood sampling (PUBS), chorionic villus sampling (CVS), and extraction of fetal cells from the maternal circulation.
- Shortly after birth, Down syndrome is diagnosed by recognizing dysmorphic features and the distinctive phenotype.
- Short stature and obesity occurs during adolescence.
- Moderate-to-severe mental retardation occurs, with an intelligence quotient (IQ) of 20 to 85 (mean, approximately 50). Hypotonia improves with age.
- Natural spontaneity, genuine warmth, cheerfulness, gentleness, patience, and tolerance are characteristics. A few patients exhibit anxiety and stubbornness.
- Infantile spasms are the most common seizures observed in infancy, whereas tonic-clonic seizures are most common in older patients.
- Decreased skin tone, early graying or loss of hair, hypogonadism, cataracts, hearing loss, age-related increase in hypothyroidism, seizures, neoplasms, degenerative vascular disease, loss of adaptive abilities, and increased risk of senile dementia of Alzheimer type are observed.
- Brachycephaly, microcephaly, a sloping forehead, a flat occiput, large fontanels with late closure, a patent metopic suture, absent frontal and sphenoid sinuses, and hypoplasia of the maxillary sinuses occur.
- Up-slanting palpebral fissures, bilateral epicanthal folds, Brushfield spots (speckled iris), refractive errors (50%), strabismus (44%), nystagmus (20%), blepharitis (33%), conjunctivitis, tearing from stenotic nasolacrimal ducts, congenital cataracts (3%), pseudopapilledema, spasm nutans, acquired lens opacity (30-60%), and keratoconus in adults are observed.
- Hypoplastic nasal bone and flat nasal bridge are typical characteristics.
- An open mouth with a tendency of tongue protrusion, a fissured and furrowed tongue, mouth breathing with drooling, a chapped lower lip, angular cheilitis, partial anodontia (50%), tooth agenesis, malformed teeth, delayed tooth eruption, microdontia (35-50%) in both the primary and secondary dentition, hypoplastic and hypocalcified teeth, malocclusion, taurodontism (0.54-5.6%), and increased periodontal destruction are noted.
- The ears are small with an overfolded helix. Chronic otitis media and hearing loss are common.
- Atlantoaxial instability (14%) can result from laxity of transverse ligaments that ordinarily hold the odontoid process close to the anterior arch of the atlas. Laxity can cause backward displacement of the odontoid process, leading to spinal cord compression in about two percent of children with Down syndrome.
- Congenital heart defects are common (40-50%); they are frequently observed in patients with Down syndrome who are hospitalized (62%) and are a common cause of death in this aneuploidy in the first two years of life. The most common congenital heart defects are endocardial cushion defect (43%), ventricular septal defect (32%), secundum atrial septal defect (10%), tetralogy of Fallot (6%), and isolated patent ductus arteriosus (4%). About 30% of patients have several cardiac defects. The most common lesions are patent ductus arteriosus (16%) and pulmonic stenosis (9%). About 70% of all endocardial cushion defects are associated with Down syndrome.
- Diastasis recti and umbilical hernia occur.
- Duodenal atresia or stenosis, Hirschsprung disease (<1%), Meckel diverticulum, imperforate anus, and omphalocele are observed. Celiac disease occurs in genetically susceptible individuals, specifically those who have the human leukocyte antigen (HLA) heterodimers DQ2 (observed in 86 to 100% of individuals with celiac disease) and DQ8. These are strong linkages with high sensitivity and poor specificity.

- Renal malformations, hypospadias, micropenis, and cryptorchidism occur.
- Short and broad hands, clinodactyly of the fifth fingers with a single flexion crease (20%), hyperextensible finger joints, increased space between the great toe and the second toe, and acquired hip dislocation (6%) are typical presentations.
 - Hashimoto thyroiditis that causes hypothyroidism is by far the most common acquired thyroid disorder in patients with Down syndrome. The onset is usually from school age onwards, but onset in infancy is reported.
 - Diabetes and decreased fertility can occur.
- Patients have about a 12-fold increased risk of infectious diseases, especially pneumonia, because of impaired cellular immunity.
- Xerosis, localized hyperkeratotic lesions, elastosis serpiginosa, alopecia areata (<10%), vitiligo, folliculitis, abscess formation, and recurrent skin infections are observed.
- Distal axial triradius in the palms, transverse palmar creases, a single flexion crease in the fifth finger, ulnar loops (often 10), a pattern in hypothenar, and interdigital III regions are observed.
- Most children with Down syndrome do not have a coexisting psychiatric or behavioral disorder. The disorders include attention deficit hyperactivity disorder, oppositional defiant disorder, nonspecific disruptive disorder, autism spectrum disorders, and stereotypical movement disorder in prepubertal children with Down syndrome and depressive illness, obsessive-compulsive disorder, and psychotic-like disorder in adolescents and adults with Down syndrome.
- Trisomy 21 mosaicism
 - Trisomy 21 mosaicism can present with absent or minimal manifestations of Down syndrome and may be underdiagnosed as a cause of early-onset Alzheimer disease.
 - The phenotype of persons having mosaicism for trisomy 21 and Down syndrome reflects the percentage of trisomic cells present in different tissues.

Management

1. Genetic counseling.
2. Vaccination and medication is recommended to prevent against secondary infections.
3. Cosmetic surgical treatment if required.

INFANTILE CORTICAL HYPEROSTOSIS

In 1945, Caffey first described infantile cortical hyperostosis, also known as Caffey disease, a self-limited disorder that affects infants and causes bone changes, soft-tissue swelling, and irritability.⁵⁷

Although the etiology of this condition is not completely understood, familial and sporadic forms appear to exist.

Infantile cortical hyperostosis is an inflammatory process of unclear etiology. In the early stages of this condition, inflammation of the periosteum and adjacent soft tissues is observed. As this resolves, the periosteum remains thickened, and subperiosteal immature lamellar bone is noted. The bone marrow spaces contain vascular fibrous tissue. Mature specimens show hyperplasia of the lamellar cortical bone without inflammation or subperiosteal changes.

CLINICAL FEATURES

- No sex predilection has been established.
- The disease may be present at birth or shortly thereafter. The familial form tends to have an earlier onset and is present at birth in 24 percent of cases, with an average age at onset of 6.8 weeks.⁵⁸ The average age at onset for the sporadic form of infantile cortical hyperostosis is 9 to 11 weeks.
- The classic presentation of infantile cortical hyperostosis includes a triad of irritability, swelling, and bone lesions.⁵⁹ The swelling appears suddenly, is deep and firm, and may be tender. Fever may occur.
- Infantile cortical hyperostosis is often multifocal and asymmetric. The disease has been described in many bones, including the mandible, tibia, ulna, clavicle, scapula, ribs, humerus, femur, fibula, skull, scapula, ilium, and metatarsal.

RADIOGRAPHIC FEATURES

Dental radiographs show an ill-defined increase in bone density with marked cortical thickening and a wavy contour. During the healing phase, a laminated periosteal reaction may be present.

HISTOPATHOLOGIC FEATURES

Lesional area shows an acute inflammatory reaction in the periosteum along with infiltration of the connective tissues by polymorphonuclear leukocytes. The process then extends to the adjacent soft tissues and muscles, resulting in collagen hyperplasia and fibrinoid degeneration. Osteoid trabeculae are formed and, during a subacute phase, the periosteum re-forms around both the old and new bone posteriorly, and it calcifies and appears subperiosteally. During the final stage, remodeling, the peripheral hyperostotic bone disappears by resorption.

Management

1. No specific treatment exists for infantile cortical hyperostosis. The disease is self-limited and usually resolves without sequelae. Some periods of exacerbation and remission may occur during the course of this condition.
2. Corticosteroids may be helpful in alleviating symptoms in severe cases, but these agents do not have any effect on the bone lesions. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also be used to treat symptoms.

MASSIVE OSTEOLYSIS (GORHAM'S DISEASE)

Gorham's Disease (GD) is an extremely rare bone disorder; fewer than 200 cases are reported in the medical literature. The etiology of Gorham disease is unknown but is thought to be related to increased vascularity of the affected bones. The resultant hyperemia has been hypothesized to uncouple the balance between osteoblasts and osteoclasts, leading to bone resorption at a far greater rate than bone formation.

CLINICAL FEATURES

- Gorham disease can present with dull, aching pain or insidious weakness, and rarely is suspected prior to radiographic evaluation.
- Patients usually are younger than 40 years.
- It is also characterized by bone loss (osteolysis) often associated with swelling or abnormal blood vessel growth (angiomatous proliferation).
- Although the disease may strike any of the bones of the body, it is more often recognized earlier when the bones at the top of the head (calvarium) and/or the mandibles are involved.

HISTOPATHOLOGIC FEATURES (FIG. 10.49)

Lesional area shows that the normal bone is replaced by connective tissue containing numerous blood vessels lined by endothelial cells.

Management

Radiation may help to control the progression and symptoms of Gorham disease, and steroids have been used with variable success.



FIGURE 10.49: Histopathologic picture of massive osteolysis showing replacement of bone by connective tissue

CEMENTOBLASTOMA

Cementoblastoma, as distinguished from cementoma, is a true neoplasm of cementum. It is a result of interruptions in or reactivation of tissues involved in the normal sequence of odontogenesis.

CLINICAL FEATURES

This benign neoplasm is rare and is usually observed in patients younger than 25 years. It is most often found in association with the apex of the mandibular first molars (50% of lesions), and it is never found in association with the anterior dentition. The lesion is usually asymptomatic, although occasionally the associated tooth may be slightly sensitive to percussion.

RADIOGRAPHIC FEATURES

A round opaque sunburst mass attached to the apex of a tooth that is well-demarcated and surrounded by a thin radiolucent rim is observed (Fig. 10.50). The lesion obscures the lamina dura. Students sometimes confuse it with condensing osteitis, a common lesion resulting from low-grade periapical irritation that stimulates bone growth. Although the most usual location for the two lesions is the same, condensing osteitis does not obscure the periodontal ligament (PDL) space and tends to be more irregular in outline. The mature cementoma, also known as periapical cemental dysplasia, is another common lesion that students may confuse with cementoblastoma. However, cementoma is usually located in the mandibular anterior region and does not obscure the PDL space. Cementomas actually have three developmental stages: osteolytic (at which point the lesion appears as a radiolucency), cementoblastic (mixed radiolucent/radiopaque), and mature (radiopaque).

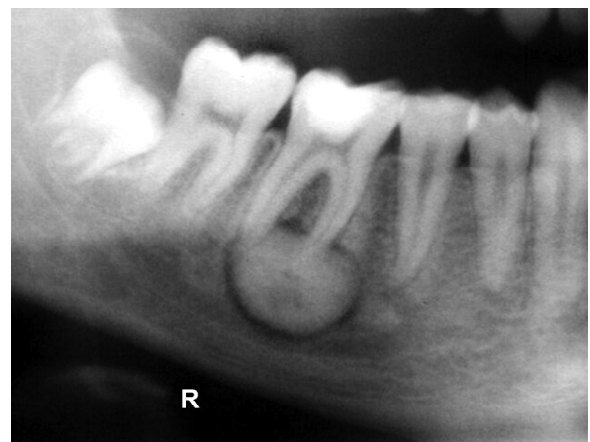


FIGURE 10.50: Cementoblastoma showing radiopaque mass attached to the root apex of tooth

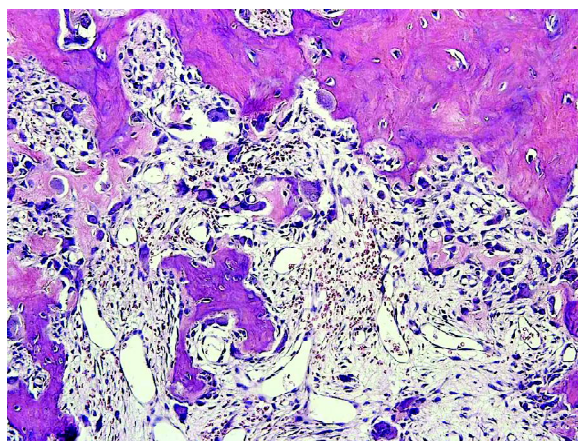


FIGURE 10.51: Histopathologic picture of cementoblastoma showing cemental trabeculae and fibrocellular connective tissue

HISTOPATHOLOGIC FEATURES (FIG. 10.51)

Plump cementoblasts separated by cemental partitions form the histology of this encapsulated lesion. Bone may show reversal lines. Connective tissue is fibrocellular. Cemental trabeculae at places show cementoblasts and cementoclasts.

Management

Removal of attached tooth and tumor is the method of treatment. No recurrences are reported.

TMJ ABNORMALITIES

APLASIA OF MANDIBULAR CONDYLE

It is failure of development of mandible. It may be unilateral or bilateral.

It mostly occurs in association with other defects such as absence of external ear, macrostomia and underdeveloped mandibular ramus.

Mandible is shifted towards the affected side.

Management of these conditions requires osetoplasty and correction of malocclusion.

HYPOPLASIA OF MANDIBULAR CONDYLE

Mandibular hypoplasia is a frequently encountered craniofacial difference and can be classified into three groups: congenital, developmental, and acquired.

Congenital form is idiopathic and may be unilateral or bilateral.

The acquired form occurs due to either forceps deliveries, external trauma to the condylar area, X-ray radiation, infections of dental origin and endocrine and vitamin derangements.

There occurs facial asymmetry, mandibular midline shift during opening and closing. Malocclusion is the common finding.

Management involves cartilage or bone transplants and unilateral or bilateral sliding osteotomy.

HYPERPLASIA OF MANDIBULAR CONDYLE

It is a rare local, unilateral enlargement of mandibular condyle. Mostly occur due to inflammation in condylar area.

Clinically, there occurs deviation of chin away from the affected side. Severe malocclusion is common finding.

Management involves resection of the mandible.

ANKYLOSIS OF TEMPOROMANDIBULAR JOINT

Bony ankylosis of the TMJ is a disabling disease that is not confined to the first two decades, but can occur later in life. Different causes have been attributed to the condition, such as condylar fracture with involvement of the articular surface, advanced arthritis and trauma from obstetric forceps. Ankylosis can be classified into true (intra-articular) and false (extra-articular).⁶⁰ TMJ ankylosis could also be classified according to type of tissue involved, bony, fibrous or fibro-osseous, or according to location, intra- or extra-capsular. If the cause is trauma, it is hypothesized that the extravasation of blood into the joint, along with the disruption of fibrocartilage integrity, permits the ingrowth of fibrous connective tissue into the joint, which subsequently results in ossification, leading to the fusion of the mandibular condyle to the articular surface of the temporal bone.⁶¹

The classic sign is the limitation of opening movement, as these patients presented. In general, patients related a history of progressive restriction of opening movement up to an unacceptable level of limitation. In some cases, the patient is hampered by a complete lack of mandibular movement. Once the movements of the TMJ are restricted; pain is not a characteristic symptom of ankylosis. Early ankylosis of the TMJ in children can be a deterrent to normal mandibular growth, resulting in a mandibular hypoplasia, especially if there is a bilateral problem. The clinical and radiographic findings are in agreement with those of Sawhney.⁶² Long-standing, early-onset ankylosis in childhood results in marked facial asymmetry, whereas the bony changes are minimal when the problem occurs during adolescence or the patient has early treatment. Osseous ankylosis presents characteristic radiographic features, which facilitate the diagnosis. In general, it is observed that the condyle is bridged with a temporal bone. It could be a small piece of bone or even a huge bone mass that could involve the condyle of the mandible, temporal bone and zygomatic process.

Management is based upon various treatment modalities such as forceful opening of jaws, condylectomy, gap arthroplasty and interposition of material for reconstruction of dead space.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a group of idiopathic disorders characterized by the proliferation of specialized, bone marrow–derived Langerhans cells (LCs) and mature eosinophils.

In 1868, Paul Langerhans discovered the epidermal dendritic cells that now bear his name.⁶³ The term Langerhans cell histiocytosis is generally preferred to the older term, histiocytosis X. This newer name emphasizes the histogenesis of the condition by specifying the type of lesional cell and removes the connotation of the unknown (X) because its cellular basis has now been clarified.⁶⁴

The working group of the Histiocyte Society has divided histiocytic disorders into three different groups: (1) dendritic cell histiocytosis, (2) erythrophagocytic macrophage disorders, and (3) malignant histiocytosis. Langerhans cell histiocytosis belongs in group 1 and encompasses a number of diseases. The clinical spectrum includes on one end an acute, fulminant, disseminated disease called Letterer-Siwe disease; and, on the other end, solitary or few, indolent and chronic lesions of bone or other organs called eosinophilic granulomas. The intermediate clinical form called Hand-Schüller-Christian disease is characterized by multifocal, chronic involvement and classically presents as the triad of diabetes insipidus, proptosis, and lytic bone lesions.

The pathogenesis of Langerhans cell histiocytosis (LCH) is unknown. An ongoing debate exists over whether this is a reactive or neoplastic process. Arguments supporting the reactive nature of this disorder include the occurrence of spontaneous remissions, the extensive elaboration of multiple cytokines by dendritic cells (DCs) and T cells (i.e. the so-called cytokine storm) in Langerhans cell histiocytosis lesions, and the good survival rate in patients without organ dysfunction.⁶⁵ Furthermore, a rigorous investigation of potential chromosomal aberrations in Langerhans cell histiocytosis via analysis of ploidy, karyotype, single-nucleotide polymorphism arrays, and array-based comparative genomic hybridization did not reveal genetic abnormalities; these findings strongly support the idea of Langerhans cell histiocytosis as a reactive process.⁶⁶

On the other hand, the infiltration of organs by a monoclonal population of aberrant cells, the possibility of lethal evolution, and the cancer-based modalities of successful treatment are all consistent with a neoplastic process.⁶⁷ In addition, the demonstration of Langerhans cell histiocytosis as a monoclonal proliferation by X chromosome-linked DNA probes supports a neoplastic origin for this proliferation; however, the presence of this finding in distinct subtypes with different evolutions demands further investigations to elucidate its significance.

In addition, some studies indicate that expression of vascular endothelial growth factor (VEGF), Bcl-2 family

proteins, and FADD, FLICE, and FLIP proteins in the Fas signaling pathway may be involved in the pathogenesis of Langerhans cell histiocytosis.⁶⁸

CLINICAL FEATURES

- Langerhans cell histiocytosis affects patients from neonates to adults, although it appears to be more common in children aged 0 to 15 years.
- Letterer-Siwe disease occurs predominantly in children younger than two years.
- The chronic multifocal form, including Hand-Schüller-Christian syndrome, has a peak of onset in children aged 2 to 10 years.
- Localized eosinophilic granuloma occurs most frequently in children aged 5 to 15 years.
- Signs of Langerhans cell histiocytosis (LCH) depend on the localization and the extent of the disease. Chronic unifocal Langerhans cell histiocytosis (eosinophilic granuloma of bone) classically presents as a solitary calvarial lesion in young adults; other frequent sites of involvement include a vertebra, rib, mandible, femur, ilium, and scapula.
- Lesions are usually asymptomatic, but bone pain and a soft tissue mass may occur.
- Bony lesions may cause otitis media by destruction of the temporal and mastoid bones, proptosis secondary to orbital masses, loose teeth from infiltration of the mandibles, or pituitary dysfunction due to involvement of the sella turcica.
- Spontaneous fractures can result from osteolytic lesions of the long bones; vertebral collapse with spinal cord compression has been described.
- Solitary cutaneous disease presents with nodulo-ulcerative lesions in the oral, perineal, perivulvar, or retroauricular regions.
- The classic multifocal form of Langerhans cell histiocytosis (Hand-Schüller-Christian disease) includes diabetes insipidus, exophthalmos, and bony defects, particularly of the cranium. Lesions may affect a variety of systems, including liver (20%), spleen (30%), and lymph nodes (50%). Pulmonary involvement may occur. Osteolytic lesions of the long bones can lead to spontaneous fractures.
- One-third of patients have mucocutaneous lesions, most frequently infiltrated nodules and ulcerated plaques, especially in the mouth, axillae, and anogenital region. Other cutaneous manifestations include extensive coalescing, scaling, or crusted papules.
- Patients with acute disseminated Langerhans cell histiocytosis (multiorgan involvement) present with fever, anemia, thrombocytopenia, pulmonary infiltrates, skin lesions, and enlargement of lymph nodes, spleen, and liver.
- The eruption may be extensive, involving the scalp, face, trunk, buttocks, and intertriginous areas. Lesions consist of closely



FIGURE 10.52: Langerhans cell histiocytosis showing crusted eruption mimicking seborrheic dermatitis

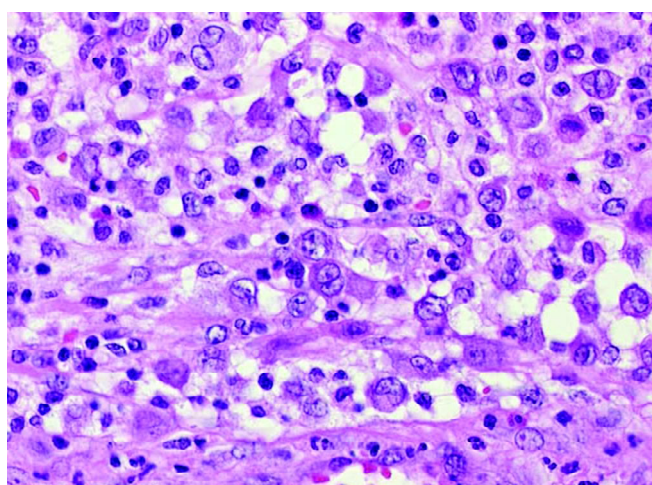


FIGURE 10.53: Histopathologic picture of Langerhans cell histiocytosis showing sheets of proliferating histiocytes

set petechiae and yellow-brown papules topped with scale and crust. The papules may coalesce to form an erythematous, weeping or crusted eruption mimicking seborrheic dermatitis (Fig. 10.52).

- Osteolytic lesions are not common in the disseminated form of Langerhans cell histiocytosis, but the mastoid can be affected, resulting in a clinical picture of otitis media, which may be the presenting complaint. Aural discharge, conductive hearing loss, and postauricular swelling have been described.
- Congenital self-healing histiocytosis presents at birth or during the early neonatal period with firm, red-brown, painless papulonodules (1–10 mm in diameter) or vesicles and crusts scattered over the scalp, face, and, to a lesser extent, trunk and the extremities. Lesions may ulcerate. Solitary lesions may occur. Lesions may be followed by residual hypopigmented or hyperpigmented macules.

HISTOPATHOLOGIC FEATURES (FIG. 10.53)

Lesional area shows a characteristic proliferation of histiocytes in the form of sheets spread diffusely throughout the microscopic field.

Management

1. The choice of therapeutic regimen is based on disease severity. The International LCH Study of the Histiocyte Society proposes the stratification of Langerhans cell histiocytosis (LCH) cases by the number of systems involved. They further categorize those cases with single-system involvement by the number of sites within that system (e.g. monostotic vs polyostotic bone disease, solitary vs multiple lymph

node involvement). In addition, the presence or the absence of organ dysfunction is used to stratify patients with multisystemic disease; the presence of any organ dysfunction portends a poorer prognosis. Treatment modalities for single-system disease includes the following:

- Solitary bone lesions are treated locally with curettage or excision.
- Painful bone lesions may require intralesional steroid injection (triamcinolone acetonide).
- Polyostotic bone lesions are best treated with indomethacin or a short course of systemic steroids.
- Bisphosphonates such as zoledronic acid can also be used to reverse bone destruction and mitigate the pain of bony lesions.
- Early treatment with vinblastine and prednisolone has been suggested for bony lesions at vital anatomic locations requiring prompt resolution.
- Rarely, lesions that are unusually large and painful occur in inaccessible sites or involve vital structures and require radiation therapy (3–6 Gy [300–600 rad]).
- Localized skin disease is best treated with moderate-to-potent topical steroids (e.g. mometasone furoate [Elocon] cream 0.1%, triamcinolone [Kenalog] cream 0.1%, fluocinolone [Synalar] ointment 0.025%) or superpotent topical steroids (e.g. clobetasol propionate 0.05%).
- In cases of severe cutaneous involvement, topical nitrogen mustard (20% solution) may be used.
- Psoralen plus ultraviolet A (PUVA) is another effective modality for cutaneous-only Langerhans cell histiocytosis or for cutaneous involvement in multisystemic disease. PUVA consists of

photosensitizing psoralens (8-methoxypsoralen or 5-methoxypsoralen) either applied topically or ingested systemically 2 hr prior to treatment with long-wave ultraviolet A (320-400 nm). The purpose of this treatment is to induce remission of skin diseases by repeated and controlled phototoxic reaction. The photoconjugation of psoralens with DNA produces an antiproliferative reaction in the skin, generates programmed cell death (apoptosis), and induces down-regulation of the cutaneous immune system.

- Ultraviolet B excimer laser has been found, in at least one case report, to offer effective adjuvant therapy in the management of cutaneous Langerhans cell histiocytosis, and it may be particularly useful for patients with comorbidities who cannot tolerate more aggressive treatment.
 - For single lymph node infiltration, excision is the treatment of choice.
 - Regional lymph node enlargement can be treated with a short course of systemic steroids.
 - Treatment-resistant nodes with sinus tracts to the skin may require systemic chemotherapy.
 - Single-agent chemotherapy with cladribine (2-CDA) may be a promising treatment for single-system pulmonary Langerhans cell histiocytosis.
2. Treatment modalities for multisystem disease includes the following:
- Systemic chemotherapy is indicated for multisystem disease and cases of single-system disease not responsive to other treatment.
 - The combination of cytotoxic drugs and systemic steroids is generally effective. Low-to-moderate doses of methotrexate, prednisone, and vinblastine are used.
 - Thalidomide has also been proposed as an agent for treating refractory/relapsing multisystem disease, but its efficacy appears to be limited to low-risk patients with only skin or bone involvement. Its use also is associated with significant toxicities, including pancytopenia and pulmonary failure.
3. Other treatment options:
- In Langerhans cell histiocytosis patients with a very poor prognosis (rapid disease progression, refractory to conventional treatment, or with disseminated risk organ involvement), bone marrow transplantation or reduced-intensity condition stem cell transplantation has shown promise as effective salvage therapy.
 - The combination of 2-chlorodeoxyadenosine (2-CDA) and cytosine arabinoside (Ara-C) has also shown promise as an effective combination therapy for refractory multisystem Langerhans cell

histiocytosis, but it is associated with considerable bone marrow toxicity.

- Resistant Langerhans cell histiocytosis may also be treated with a combination of cyclosporin A, antithymocyte globulin, and prednisolone if patients do not have a matched donor for bone marrow transplantation.
- Other potential treatments include monoclonal antibody targeting with indium In-labeled anti-CD1a, cytokine inhibitors, alemtuzumab, and all-*trans* retinoic acid.
- Diabetes insipidus is treated symptomatically with desmopressin acetate (DDAVP).

HAND-SCHÜLLER-CHRISTIAN DISEASE

In Hand-Schüller-Christian disease, abnormal scavenger cells called histiocytes and eosinophils (another immune system cell type) grow uncontrollably, proliferating usually in the lungs and bone, often forming scars that interfere with normal functioning. These cells constitute malignant or benign macrophages in the tissues, or Langerhans' cells in the bone marrow.

This syndrome is characterized by three, simultaneous conditions:

- Diabetes insipidus
- Exophthalmus
- Destructive Bone Lesions.

Diabetes insipidus is a condition in which the body fails to produce the hormone vasopressin (anti-diuretic hormone), or the kidneys fail to use vasopressin properly. The result is loss of large volumes of water through excretion (urination). Exophthalmos means protrusion of the globe of the eye (i.e. the "eyeball" protrudes). It is caused by damage to the pituitary gland.

Radiographic findings show severe bilateral loss of bone in maxilla and mandible (Fig. 10.54). 'Scooped out' lesions of bones are seen. Sometimes, teeth appear floating in air.



FIGURE 10.54: Hand-Schüller-Christian disease showing severe bone loss occurring bilaterally in maxilla and mandible

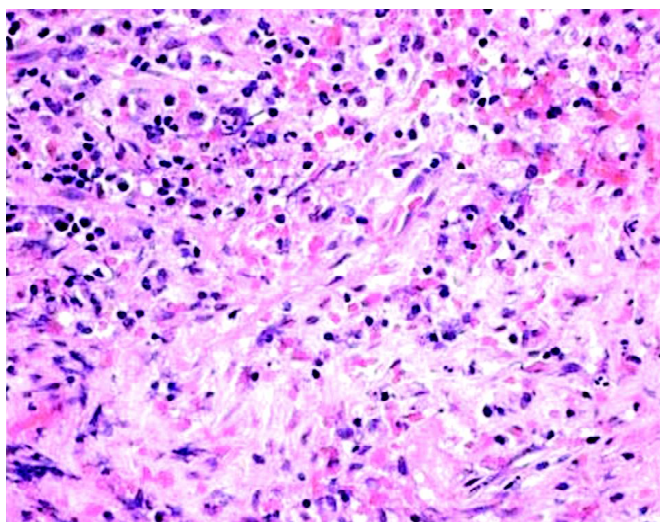


FIGURE 10.55: Histopathological picture of Hand-Schüller-Christian disease showing diffuse infiltrate of pale staining histiocytes interspersed within lymphocytes, plasma cells

HISTOPATHOLOGIC FEATURES

- Lesional areas show diffuse infiltrate of pale staining histiocytes interspersed within lymphocytes, plasma cells and often eosinophils (Fig. 10.55).
- Hand-Schüller-Christian syndrome often occurs with lymphoma, carcinoma, and multifocal eosinophilic granuloma (it occurs in 25% of all cases of multifocal eosinophilic granuloma).
- Treatment involves treating the underlying cause, such as lymphoma, and manifestations, such as diabetes insipidus.

EOSINOPHILIC GRANULOMA

Lichtenstein and Jaffe, 1940, introduced the term Eosinophilic granuloma.⁶⁹

CLINICAL FEATURES

- Clinically no signs and symptoms are seen except fever and malaise.
- There may be localized pain and swelling.
- Lesion occurs in skull and jaws. Other sites involved are long bones, ribs, humerus etc.
- It appears brownish to grayish in color.

RADIOLOGICAL FEATURES

Radiographically, the lesion appears localized well-circumscribed, irregular and radiolucent area.

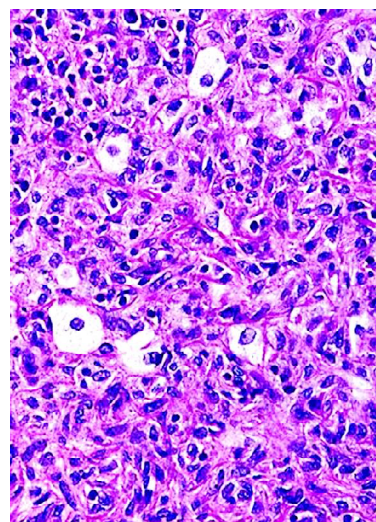


FIGURE 10.56: Histopathologic picture of eosinophilic granuloma showing diffuse sheet-like collection of histiocytes

HISTOPATHOLOGIC FEATURES (FIG. 10.56)

- Lesional areas show diffuse sheet-like collection of histiocytes interspersed with lymphocytes, plasma cells and eosinophils.
- Eosinophils decrease in number as the lesion matures.

Management

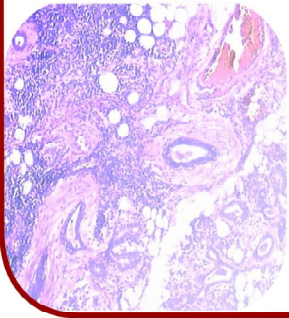
1. Curettage and X-ray therapy are curative.
2. Symptoms subside within two weeks after treatment.

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Salivary Gland Lesions in Children

Mayur Chaudhary, Shweta Dixit Chaudhary

CHAPTER OVERVIEW

Introduction

Classification

Developmental disturbances of salivary glands in children:

Aplasia

Xerostomia

Hyperplasia of palatal salivary glands

Atresia

Diverticuli

Aberrancy

Developmental lingual salivary gland depression

Heterotropic salivary glands

Accessory parotid glands

Adenomatoid hyperplasia of mucous glands

Polycystic (dysgenetic) disease of the parotid glands

Sialadenitis

Sarcoidosis

Sialolithiasis

Benign neoplasms:

Pleomorphic adenoma

Warthin's tumor

Malignant neoplasms:

Mucoepidermoid carcinoma

Acinic cell adenocarcinoma

INTRODUCTION

Salivary glands are divided into major and minor salivary gland categories. The major salivary glands are the parotid, the submandibular and the sublingual glands. The minor glands are dispersed throughout the upper aerodigestive submucosa (i.e. palate, lip, pharynx, nasopharynx, larynx, parapharyngeal space).

Salivary gland diseases represent a disparate group of disorders affecting both the major and minor salivary glands. These conditions range from inflammatory disorders of infectious, granulomatous, or autoimmune etiology to obstructive, developmental and idiopathic disorders and certain neoplasms (either benign or malignant). The major salivary glands are most often involved and many of these salivary gland disorders are associated with the presence of other systemic illnesses. A thorough history and physical examination is typically adequate to recognize and differentiate this group of conditions and an elaborate diagnostic evaluation is usually not required to manage these illnesses.

CLASSIFICATION

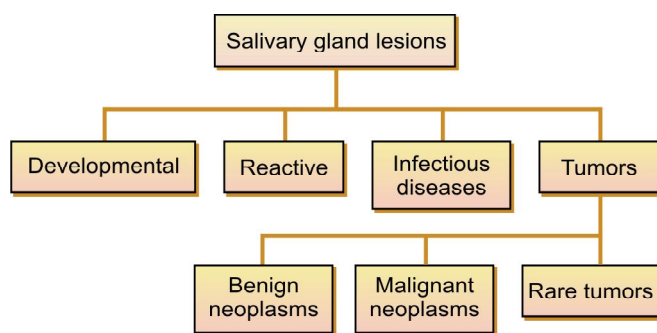
Salivary Gland Lesions (Fig. 11.1)

Developmental disturbances

- Aplasia
- Xerostomia
- Hyperplasia of parotid glands
- Atresia
- Abberancy
- Developmental lingual mandibular salivary gland depression
- Heterotropic salivary glands
- Accessory parotid glands
- Adenomatoid hyperplasia of mucous glands
- Polycystic disease of parotid gland.

Reactive lesions

- Mucous extravasation phenomenon
- Mucous retention cyst
- Pseudocyst (mucous retention cyst)
- Necrotizing sialometaplasia
- Adenomatoid hyperplasia

FIGURE 11.1: Classification of salivary gland lesions¹*Infectious diseases*

- Mumps
- Cytomegalovirus sialadenitis
- Bacterial sialadenitis
- Sarcoidosis
- Metabolic conditions
- Sjögren's syndrome
- Salivary lymphoepithelial lesion

Sjögren's syndrome is now considered under autoimmune disorders.

Benign neoplasms

- Mixed tumor (Pleomorphic adenoma)
- Monomorphic adenoma
- Myoepithelioma
- Ductal papillomas
- Warthin's tumor (papillary cystadenoma lymphomatosum).

Malignant neoplasms

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Polymorphous low grade carcinoma
- Clear cell carcinoma
- Adenocarcinoma not otherwise specified.

Rare tumors

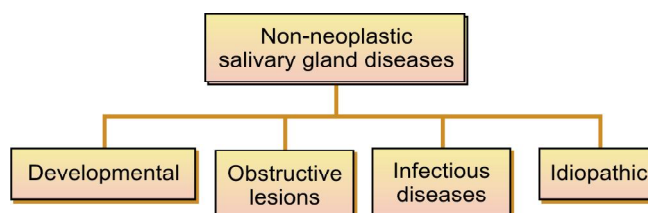
- Epimyoeplithelial carcinoma
- Salivary duct carcinoma
- Basal cell adenocarcinoma
- Squamous cell carcinoma.

Non-neoplastic Salivary Gland Diseases (Fig. 11.2)

Ellis, Auclair and Gnepp² have classified non neoplastic salivary gland diseases as follows:

Developmental disturbances

- Aplasia
- Xerostomia
- Hyperplasia of palatal salivary glands
- Atresia

FIGURE 11.2: Classification of non-neoplastic salivary gland diseases²

- Abberancy
- Developmental lingual salivary gland depression
- Heterotropic salivary glands
- Accessory parotid glands
- Adenomatoid hyperplasia of mucous glands
- Polycystic disease of parotid gland.

Obstructive lesions

- Mucous escape reaction
- Mucous retention reaction
- Sialolithiasis.

Infectious diseases

- Tuberculosis
- Cat scratch disease
- Salivary gland cyst as manifestation of AIDS
- Cytomegaloviral infection
- Mumps
- Sarcoidosis.

Idiopathic

- Necrotizing sialometaplasia
- Benign cysts of parotid glands
 - Lymphoepithelial cyst
 - Salivary duct cyst
- Angiolymphoid hyperplasia with eosinophilia and Kimura's disease
- Cheilitis glandularis
- Benign lymphoepithelial lesion and Sjögren's syndrome.

DEVELOPMENTAL DISTURBANCES OF SALIVARY GLANDS IN CHILDREN

APLASIA

Aplasia is also called as agenesis. In this condition, any one or a group of salivary glands may be congenitally absent, unilaterally or bilaterally. It was first described by Gruber, 1885. It may occur in association with other developmental abnormalities such as atresia of lachrymal puncta and congenital

malformation of the temporomandibular component. It may also occur in conjunction with other developmental defects such as hemifacial microsomia, Lachrymal Auricular Dental Digital syndrome (LADD syndrome), mandibulofacial dysostosis (Treacher Collins syndrome).

ETIOLOGY

- Local disturbance in early fetal development.
- **Mc Donald et al**, 1986, suggested an ectodermal origin for this anomaly.³

CLINICAL FEATURES

- Initial manifestation may be development of xerostomia and its sequelae.
- CT scan or MRI help in the diagnosis by indicating absence of the gland and its replacement by fat and fibrous tissue.
- Scintiscanning with a radioisotope may be used for confirmation of the diagnosis.
- Absence of the salivary duct orifice/papilla may be one of the indicators of aplasia.
- Patient may present with increased caries, burning sensation, oral infections and taste aberrations due to absence of saliva.
- Xerostomia may also necessitate constant sipping of water throughout the day and cause difficulty in swallowing at meal times.
- Oral mucosa appears dry, smooth or sometimes pebbly and shows a tendency for accumulation of debris.
- Cracking of lips and fissuring of the corners of the mouth may be seen.
- Although hypoplasia of salivary glands is rare, hypoplasia of parotid gland has been reported to be present with Melkersson-Rosenthal syndrome.
- **Hemifacial microsomia:**
 - Incidence is 1 in 3500 births.
 - Asymmetric, mild to severe underdevelopment of the craniofacial skeleton, the external ear and facial soft tissues including the parotid gland is seen.
 - Usually involves structures derived from the first and second branchial arch.
 - Usually sporadic in nature.
- **LADD syndrome:**
 - Follows the autosomal dominant mode of inheritance.
 - L—lachrymal apparatus may show occlusion of the lachrymal puncta, nasolachrymal duct obstruction with overflow of tears (epiphora), lachrymal sac inflammation (dacrocystitis) and lachrymal gland aplasia.
 - A—auricles are deformed with the ear having a cup shaped appearance alongwith some hearing loss.

- D—dentally, peg shaped teeth, hypodontia and enamel hypoplasia may be seen.
- D—digital deformities may present as deviation of the fingers medially or laterally (clinodactyly).
- **Mandibulofacial dysostosis:**
 - Usually familial in origin following an irregular form of dominant transmission.
 - Rare; incidence being 1 in 25,000 to 1 in 50,000.
 - Symmetric notching of the lower eyelids with eyes slanting downwards at the lateral borders (anti-mongoloid palpebral fissures).
 - Hypoplasia of facial bones, especially, malar bones and mandible.
 - Malformation of the external ear.
 - Macrostomia, high palate, malocclusion of teeth.
 - Salivary aplasia.
 - Characteristic facies referred to as bird-like or fish-like in nature.

Management

1. Treatment is primarily supportive in nature.
2. Primary aim is to relieve xerostomia by the use of salivary substitutes, frequent mouthwashes, comprehensive dental care, fluoride therapy and good oral hygiene.

XEROSTOMIA

The term xerostomia was first described by **Bartley in 1868** and stands for the Greek terminology of *xeros* means dry and *stoma* means mouth.⁴

Xerostomia is defined as dry mouth resulting from reduced or absent salivary flow. Xerostomia is not a disease, but it may be a symptom of various medical conditions. Although usually said to be common in almost 20 percent of the geriatric population, it is important to bear in mind that xerostomia can occur in any age group. Its occurrence is not related as much to age as the causative factor, disease, radiation or medication taken by a particular individual. However, it is not very common in the pediatric age group.

NORMAL SALIVARY FUNCTION

Normal salivary function is mediated by the muscarinic M3 receptor. Stimulation of this receptor results in increased watery flow of salivary secretions. When the oral mucosal surface is stimulated, afferent nerve signals travel to the salivatory nuclei in the medulla. The medullary signal may also be affected by cortical inputs resulting from stimuli such as taste, smell, anxiety or depression. Efferent nerve signals, mediated by acetylcholine, also stimulate salivary glandular epithelial cells and increase salivary secretions.⁵

ETIOLOGY

Developmental conditions such as aplasia, agenesis of the salivary glands or a deficiency of the M3 receptors or chronic administration of anticholinergic or parasympatholytic drugs may lead to signs and symptoms of xerostomia.

Radiotherapy in cancer patients is one of the most common causes of xerostomia. However, since radiotherapy can prevent the normal growth and development of bones, muscles and other tissues, most cancer specialists avoid radiotherapy or use the lowest possible doses of radiation when caring for children with carcinomas.

A number of medications can cause xerostomia, including many drugs used in the management of cancer or cancer treatment side effects. Some of these are: atropine (used with caution in children), carbamazepine (used with caution in children), diphenhydramine (used with caution in children), haloperidol, loperamide (used with caution in children), and scopolamine (used with caution in children), among several others.

Xerostomia may develop in children with HIV infection, as the virus often damages the salivary glands.

Diseases like sarcoidosis, rheumatoid arthritis, thyroid dysfunction may also result in sialadenitis and reduction in salivary flow.

CLINICAL FEATURES

Xerostomia can cause a derangement in the nutritional, dental as well as psychological health of the affected individual. The following features may be present:

- Dryness of the mouth
- Cracked lips, cuts, or cracks at the corners of the mouth.
- Taste changes (dysgeusia)
- A burning sensation of the tongue, painful tongue (glossodynia)
- Changes in the surface of the tongue
- Constant sore throat
- Hoarseness and/ or dry nasal passages
- Difficulty wearing dental appliances (like space maintainers, myofunctional appliances)
- Difficulty swallowing fluids accompanied by an increase in thirst
- Difficulty in eating especially dry, crumbly foods
- Development of gum disease and cavities
- Development of candidiasis, sialadenitis
- Development of halitosis.

Xerostomia causes the following mouth changes that can contribute to discomfort for the patient and an increased risk for oral lesions:

- Saliva becomes thick and is less able to lubricate the mouth.
- Acids in the mouth cannot be neutralized, leading to mineral loss from the teeth

- The acid produced after eating or drinking sugary foods leads to further mineral loss from the teeth, causing even more tooth decay
- There is an increased risk of cavities because the mouth is less able to control bacteria
- Plaque becomes thicker and heavier because of the patient's difficulty in maintaining good oral hygiene.

DIAGNOSIS AND EVALUATION OF XEROSTOMIA

Diagnosis of xerostomia may be based on evidence obtained from the patient's history, an examination of the oral cavity and/or sialometry, a simple office procedure that measures the flow rate of saliva. Xerostomia should be considered if the patient complains of dry mouth, particularly at night, or of difficulty eating dry foods such as crackers.^{6,7} When the mouth is examined, a tongue depressor may stick to the buccal mucosa.⁸ When wearing lipstick, the "lipstick sign," where lipstick adheres to the front teeth, may be a useful indicator of xerostomia.

The oral mucosa may be dry and sticky, or it may appear erythematous due to an overgrowth of *Candida albicans*. The red patches often affect the hard and soft palate and dorsal surface of the tongue. Occasionally, pseudomembranous candidiasis may be present, appearing as removable white plaques on any mucosal surface. There may be little or no pooled saliva in the floor of the mouth and the tongue may appear dry with decreased numbers of papillae. The saliva may appear stringy, ropy or foamy. Dental caries may be found at the cervical margin or neck of the teeth, the incisal margins or the tips of the teeth.⁶

Several office tests and techniques can be utilized to ascertain the function of salivary glands. In sialometry, or salivary flow measurement, collection devices are placed over the parotid gland or the submandibular/sublingual gland duct orifices and saliva is stimulated with citric acid. The normal salivary flow rate for unstimulated saliva from the parotid gland is 0.4 to 1.5 ml/min/gland. The normal flow rate for unstimulated, "resting" whole saliva is 0.3 to 0.5 ml/min; for stimulated saliva, 1 to 2 ml/min. Values less than 0.1 ml/min are typically considered xerostomic, although reduced flow may not always be associated with complaints of dryness.⁷

Sialography is an imaging technique that may be useful in identifying salivary gland stones and masses. It involves the injection of radio-opaque media into the salivary glands. Salivary scintigraphy can be useful in assessing salivary gland function. Technetium-99m sodium pertechnetate is intravenously injected to ascertain the rate and density of uptake and the time of excretion in the mouth.⁹

Management

Identification of the underlying cause is the first step when it comes to management of xerostomia. Xerostomia usually cannot be reversed when the cause is a developmental disorder like aplasia or agenesis or the destruction of the salivary glands by radiation treatment. It may be reversible if related to a medication. All of the treatment measures serve to increase the level of comfort, decrease the chance for oral lesions and reduce the occurrence of gum disease and cavities.

1. Cleaning the mouth well at least four times per day (after every meal and at bedtime).
2. Rinsing the mouth immediately after every meal.
3. Sipping water frequently.
4. Rinsing the mouth with a salt and baking soda solution four to six times per day (1/2 tsp salt, 1/2 tsp baking soda, and 8 oz of water).
5. Chlorhexidine rinses may also be useful in preventing caries by reducing lactobacillus counts in the mouth.
6. Avoiding foods and liquids containing large amounts of sugar as well as irritating foods that are dry, spicy, astringent or excessively hot or cold.
7. Avoiding mouthwashes containing alcohol.
8. Using moisturizer and lubricants such as orajel® or vaseline® and glycerin swabs on the lips.
9. Using saliva substitutes which offer a replacement therapy to help relieve discomfort. Commercially available products come in a variety of formulations including solutions, sprays, gels and lozenges. In general, they contain an agent to increase viscosity, such as carboxymethylcellulose or hydroxyethylcellulose, minerals such as calcium and phosphate ions and fluoride, preservatives such as methyl- or propylparaben, and flavoring and related agents.

Carboxymethyl or hydroxycellulose solutions:

- Entertainer's secret® (KLI Corp), spray
- Glandosane ® (Kenwood/ Bradley) spray
- Moi-Stir® (Kingswood Labs) spray
- Moi-Stir® oral swabsticks (Kingswood Labs) swabs
- Optimoist® (Colgate-Palmolive) spray
- Saliva substitute® (Roxane Labs) liquid
- Salivart® (Gebauer) preservative-free aerosol
- Salix® (Scandinavian Natural Health and Beauty) tablets
- VA oralube® (Oral Dis. Res. Lab) sodium-free; liquid
- Xero-Lube® artificial saliva (Scherer) sodium-free; spray

Mucopolysaccharide solutions:

Mouthkote ® (Parnell) spray

10. Using a sialogogue such as pilocarpine (Salagen), Cevimeline (cholinergic agonist), yohimbine (alpha-2

adrenergic antagonist), human interferon alfa (IFN- α) or sugarless candies and chewing gum which can stimulate saliva secretion from the remaining salivary glands. Eating foods such as carrots or celery may also help patients with residual salivary gland function. Saliva stimulants like Natrol dry mouth relief (anhydrous crystalline maltose) may help in stimulating saliva production.

11. Applying a prescription-strength fluoride gel daily at bedtime to clean the teeth.
12. A cold air humidifier may aid mouth breathers who typically have their worst symptoms at night.
13. Addition of flavor enhancers such as herbs, condiments and fruit extracts may make food more palatable to patients complaining of their food tasting bland, papery, salty or otherwise unpleasant.
14. Using low abrasive fluoride toothpaste to brush the teeth. Biotene® and oralbalance® dentifrices are available over-the-counter from Laclede, Inc. These are antixerostomia dentifrices that contain three salivary enzymes, lactoperoxidase, glucose oxidase and lysozyme, specifically formulated to activate intra-oral bacterial systems.
15. Symptoms of xerostomia are often worse between meals, at night and in the morning. Therefore, consider modifying drug schedules to achieve maximum plasma levels when the patient is awake. Consider easy-to-take formulations, such as liquids and avoid sublingual dosage forms if possible.

HYPERPLASIA OF PALATAL SALIVARY GLANDS

Giansanti et al, 1971, reported unusual localized hyperplasia or hypertrophy of minor accessory salivary glands in the palate.¹⁰

ETIOLOGY

Unknown, but the following have been reported to result in salivary gland enlargement:

- Hormonal disorders: Endocrine disorders, menopause.
- Metabolic disorders: Gout, diabetes mellitus.
- Autoimmune disorders: Sjögren's syndrome, Waldenstrom macroglobulinemia.
- Syndromes: Aglossia-adactylia syndrome, Heerfordt's syndrome, Felt's syndrome.
- Miscellaneous: Hepatic disease, starvation, alcoholism, inflammation, benign lymphoepithelial lesion, adiposity, hyperthermia, oligomenorrhea and certain drugs.
- Of these menopause, diabetes mellitus, Sjögren's syndrome, Waldenstrom macroglobulinemia, Heerfordt's syndrome, Felt's syndrome, alcoholism, benign lymphoepithelial lesion, adiposity, hyperthermia, oligomenorrhea are usually not seen in the pediatric population.

CLINICAL FEATURES

- Usually asymptomatic.
- Usually involves the minor salivary glands of the palate.
- Presents as a small localized swelling measuring from several millimeters to around a centimeter in diameter, usually on the hard palate or at the junction of the hard and the soft palate. The lesion has an intact surface and is firm, sessile and normal in color.
- Age and gender predilection have not been established as yet.
- *Arafat et al, 1981*,¹¹ reported 10 cases of salivary gland hyperplasia. There were no associated abnormalities and no evident causative factors. Contrary to previous reports, one of their cases involved the glands of the retromolar area rather than the palate.

HISTOPATHOLOGIC FEATURES

- The histopathologic picture does not differ significantly from normal mucous gland structure.
- Closely packed collections of normal appearing mucous acini with the usual intermingling of normal ducts is seen.
- There is no inflammation, no spillage of mucin and no fibrosis.

Management

1. Primary mode of treatment is an excision biopsy for microscopic examination as the lesion could also be a salivary gland neoplasm of the area.
2. Recurrence has not been reported as yet.

ATRESIA

It is the congenital occlusion or absence of one or more of the major salivary gland ducts.

- It is an exceedingly rare condition.
- Usually the submandibular duct in the floor of the mouth fails to canulate during embryological development.
- Within two to three days of age, the newborn infant presents with submandibular swelling on the affected side due to the presence of a retention cyst.
- A relatively severe xerostomia may also be present.

DIVERTICULI

A diverticulum is an outpouching of the ductal system of one of the major salivary glands. Its clinical significance lies in the fact that it may lead to recurrent episodes of acute parotitis.

ABERRANCY

Aberrancy is simply that situation in which salivary glands are found farther than normal from their usual location. The normal accessory salivary glands in the oral cavity have such a widespread distribution that it is really difficult to pinpoint the condition of aberrancy. Fortunately, the only clinical significance aberrant salivary glands may have is that they may be the site of development of a retention cyst or a neoplasm. Cases have been reported in which salivary gland tissue has been found within the body of the mandible. This condition known as the “developmental lingual mandibular salivary gland depression” has been described separately.

DEVELOPMENTAL LINGUAL SALIVARY GLAND DEPRESSION

Also known as Stafne cyst/defect, static bone cyst, latent bone cyst, static bone cavity, lingual mandibular bone cavity. The developmental lingual mandibular salivary gland depression is an unusual form of slightly aberrant salivary gland tissue wherein a developmental inclusion of glandular tissue is found within, or more commonly, adjacent to the lingual surface of the body of the mandible within a deep and well-circumscribed depression. This entity is named after Stafne who first recognized this phenomenon in 1942.¹² However, the oldest description is in a skull dated to the sixth to fourth century B.C.

CLINICAL FEATURES

- Incidence is 0.1 to 1.3 percent.
- Predilection of males over females is seen.
- Although it is a congenital defect, it is not very commonly observed in children.
- The radiograph reveals an ovoid radiolucency located between the inferior alveolar canal and the inferior border of the mandible in the region of second or third molars (Fig. 11.3).

DIAGNOSIS

- Differential diagnosis includes the traumatic or hemorrhagic bone cyst from which it can be differentiated by the location of the traumatic bone cyst superior to the inferior alveolar canal.
- A rare anterior variant of the Stafne’s cyst has also been reported presenting as a round or ovoid radiolucency in the area between the central incisors and first premolars.



FIGURE 11.3: Ovoid radiolucency located between the inferior alveolar canal and the inferior border of the mandible

HETEROTROPIC SALIVARY GLANDS

Heterotropic salivary glands are also referred to as ectopic salivary gland tissue or salivary gland choristomas. They include the salivary gland tissue located at sites other than those appropriate for normal anatomic distribution of the major salivary glands, oral mucosa and pharynx.

ETIOLOGY

- Embryogenesis of the heterotropic salivary gland tissue is often unclear and is related to the anatomic site.
- **Willis, 1968**, has proposed three general explanations for heterotropia:¹³
 1. Abnormal persistence and development of vestigial structures.
 2. Dislocation of a portion of a definitive organ rudiment during mass movement of development.
 3. Heteroplasia which is abnormal differentiation of the local tissues.

SITE

- The most common locations are the paraparotid lymph nodes, middle ear and lower neck.
- Less frequent locations are the upper neck, mandible, external auditory canal, mediastinum, cerebellopontine angle, pituitary gland, prostate gland, vulva, rectum, thyroglossal duct, thyroid gland and parathyroid capsules.

CLINICAL FEATURES

- According to a survey of 20,000 salivary gland lesions by the Armed Forces Institute of Pathology (AFIP),¹⁴

heterotropic salivary gland tissue was considered to have given rise to tumors in 12 percent of the 110 cases of heterotropic tissue. When heterotropia was associated with a salivary gland tumor, the majority were mucoepidermoid carcinomas (46%). The others were mixed tumors (23%), Warthin's tumor (23%) and adenoma (8%).

- Heterotropic salivary gland tissue in the paraparotid area shows intranodal occurrence easily explained by the entrapment of salivary gland tissue in lymph nodes during embryonic development.
- The propensity for occurrence in the paraparotid nodes could be related to the latent encapsulation of the parotid glands. However, **Bernier and Bhaskar, 1978**,¹⁵ and **Azzopardi and Hou, 1964**,¹⁶ have argued over whether salivary gland tissue in paraparotid lymph nodes is true heterotropia rather than a variation of normal tissue.

HISTOPATHOLOGIC FEATURES

- **Histopathologically**, the tissue mainly consists of either mixed seromucinous glands or more commonly serous glands with randomly scattered well-formed ducts.
- It is important not to interpret a well-differentiated metastatic tumor in paraparotid nodes as heterotropic salivary gland tissue.

HETEROTROPIC SALIVARY GLAND TISSUE OF THE LOWER NECK

CLINICAL FEATURES

- Heterotropic salivary gland tissue of the lower neck has a unique clinical presentation, but unexplained embryogenesis.
- Usually presents as branchial cleft sinuses in the lower anterolateral neck, medial to the border of the sternocleidomastoid muscle.
- Bilateral presentation, as well as, existence at birth is a common feature.
- Most characteristic feature is presence of a draining sinus that secretes a mucoid, creamy or clear saliva like fluid. Drainage is minimal but may increase at meal times.
- The sinus tract is usually less than 2 cm and emanates from a nodular or lobulated gray or yellow soft tissue mass, which occasionally resembles normal salivary gland tissue.
- Swelling may be apparent.
- Some lesions present as deep seated cysts that communicate through the sinus.

HISTOPATHOLOGIC FEATURES

- Histopathologically, the sinus may be lined by pseudo-stratified ciliated columnar epithelium with metaplastic stratified squamous epithelium. The heterotropic salivary

gland tissue may be identical with normal oral salivary gland tissue and thus, may contain serous, mucous or mixed glandular acini. Cartilage may also be present and is possibly attributed to branchial origin.

- **Youngs and Scofield, 1967**,¹⁷ proposed that ectopic salivary gland tissue in the lower neck results from the overgrowth of the second branchial arch, which overlaps the second, third and fourth branchial clefts, thus forming the precervical sinus of His.
- **Himalstein, 1981**, has suggested that this tissue is a residuum of the tenth nerve ganglion placodal duct after the sinus of His has dissipated.¹⁸

HETEROTROPIC SALIVARY GLAND TISSUE OF THE MIDDLE EAR

CLINICAL FEATURES

- Heterotropic salivary gland tissue of the middle ear was first reported by **Taylor and Martin, 1961**.¹⁹
- Its pathogenesis is thought to be related to errant development of the first and second branchial arches at some time before the fourth month of intrauterine life.
- It is quite a rare lesion and presents with unilateral conductive hearing loss.
- Usually presents in the first and second decades of life arising in close association with the facial nerve.
- Ossicle deformities (mainly incus and stapes), cholesteatomas and oval window absence are seen.
- Usually appears as a gray to yellow, lobulated or smooth surfaced, soft mass that is approximal to the facial nerve.

HISTOPATHOLOGIC FEATURES

- Histopathologically, mixed serous and mucous glands are seen with excretory ducts in some cases. The salivary gland elements are intermixed with mature adipose tissue and loosely arranged fibrous connective tissue.
- Although recurrence is minimal, careful dissection is recommended to avoid damage to the facial nerve.

INTRAOSSEOUS HETEROTROPIC SALIVARY GLAND TISSUE

CLINICAL FEATURES

- Intraosseous heterotropic salivary gland tissue is usually found in close association with the mandible and occurs in crypt like invaginations of the lingual surface
- First described by **Staffne in 1942**,¹² and has been discussed previously in this section
- Pathogenesis for this lesion could be embryonic, congenital, aneurysmal or developmental

- However, cases involving children have been documented with no cases reported by **Uemura et al, 1976**.²⁰

HISTOPATHOLOGIC FEATURES

Histopathologically, the tissue is primarily mucous acini and some cases are contiguous with the sublingual gland.

HETEROTROPIC SALIVARY GLAND TISSUE OF OTHER SITES

CLINICAL FEATURES

- Heterotropic salivary gland tissue of other sites include gingival choristomas which manifest as yellow swellings at the mucogingival junction and are composed of seromucous or pure mucous glands.
- May arise from pluripotential gingival epithelium or from a mechanical disturbance during development.
- Likewise, rare cases of heterotropic salivary gland tissue have been reported at the cerebellopontine angle, external auditory canal, posterior lobe of the pituitary, mediastinal lymph node, rectum and vulva.

Heterotropia and associated salivary gland tumors refers to the numerous examples of salivary gland tumors originating in heterotropic salivary gland tissue. These tumors include acinic cell carcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, monomorphic adenoma and mixed tumor.

ACCESSORY PAROTID GLANDS

The term accessory parotid glands refers to lobules of parotid salivary tissue that are separated from the main body of the gland but that drain into Stenson's duct.

CLINICAL FEATURES

- Typically ranges from 0.5 to 3 cm and may be spherical or oblong.
- The accessory parotid tissue is usually bound to the fascia of the masseter muscle at an average distance of 6mm from the anterior edge of the parotid gland usually on or above the duct.
- Usually seen anterior to the border of the masseter, resting on the buccal pad fat.
- This parotid tissue is normally connected to Stenson's duct by a single accessory duct, but there may be 2 to 10 ducts.
- **Frommer, 1977**, showed that 21 percent out of 96 cadaver dissections demonstrated accessory parotid salivary gland tissue. He also pointed out that anterior extensions of parotid gland tissue along the parotid duct are normal variants of the parotid gland tissue and should not be considered as accessory tissue.²¹

- Clinically present as masses in the cheek that occur in the central third of a line drawn from the middle of the tragus to a point midway between the ala of the nose and the vermillion border of the upper lip.
- The primary clinical significance of the recognition of accessory parotid tissue is that any pathologic process that can occur in the main gland can also occur in the accessory tissue and incorrect diagnosis may lead to inadequate treatment.
- **Perzik and White, 1966**, reported that in 7.7 percent of 591 parotid tumors, an accessory parotid gland was involved.²²
- The most common malignant salivary gland neoplasm in accessory parotid tissue has been low grade mucoepidermoid carcinoma. Intermediate and high grade mucoepidermoid carcinoma, acinic cell carcinoma, malignant mixed tumor and adenoid cystic carcinoma have also been reported.
- The most common benign salivary gland neoplasm in accessory parotid tissue has been a mixed tumor although cases of Warthin's tumor and papillary cystadenoma have occurred.
- Sialography and palpation of the area while passing a lachrymal probe through the Stenson's duct may be used in the diagnosis of accessory parotid salivary gland lesions.

HISTOPATHOLOGIC FEATURES

Histopathologically, the tissue is identical to the primary parotid tissue of the individual. Histological character of the neoplasm developing in the accessory salivary gland tissue is identical to that seen in lesions arising in the gland proper.

Management

1. Primary surgical management of lesions of accessory parotid tissue must include complete removal, acceptable cosmetic result, avoidance of external salivary fistulas and preservation of the buccozygomatic rami of the facial nerve.
2. **Polayes and Rankow, 1979**, recommend a standard preauriculocervical flap that gives adequate exposure for a superficial or total parotidectomy and that provides an opportunity to preserve facial nerve function.²³
3. For high grade malignancy, they recommend total parotidectomy with excision of the accessory gland.
4. For inflammatory or benign lesions, they recommend excision of the accessory gland or excision of the accessory gland and superficial parotidectomy.

ADENOMATOID HYPERPLASIA OF MUCOUS GLANDS

Adenomatoid hyperplasia of mucous glands was described by **Arafat et al, 1981**, as representing a hyperplastic phenomenon or a hamartomatous proliferation.²⁴ However, **Aufdemorte et al, 1985**, argued that since adenomatoid hyperplasia does not

fulfill the histologic criteria of an adenoma, it should not be called so.²⁵ Interestingly, a lot of authors have used the term adenomatoid hyperplasia.

CLINICAL FEATURES

- Occurs in the age range of 5 to 81 years. However, usually found in middle aged group with an average age of 41.7 years.
- Male predilection has been reported.
- Usually presents as an asymptomatic palatal mass that is not ulcerated and that is normal or bluish in color.
- Generally firm and sessile, although, has been variously reported as soft or hard.

HISTOPATHOLOGIC FEATURES

- Mucosa appears normal although pseudoepitheliomatous hyperplasia has been reported.
- Underlying connective tissue contains enlarged lobules of normal appearing mucous acini and ducts.
- Salivary gland tissue has been described as hyperplastic, present in greater than normal amounts and crowded.
- Inflammation and fibrosis are not significant features.
- **Aufdemorte et al, 1985**, reported that cytologic features of fine needle aspirate of adenomatoid hyperplasia resemble low grade mucoepidermoid carcinoma and cautioned that misinterpretation may result in inappropriate treatment.²⁵

Management

1. Total excision of the lesion is recommended.
2. Recurrence is not expected.
3. However, association with mucoepidermoid carcinoma has been suggested.
4. **Arafat et al, 1981**, reported a patient in whom mucoepidermoid carcinoma developed twelve years after the patient was diagnosed with mucinous salivary gland hyperplasia.²⁴

POLYCYSTIC (DYSGENETIC) DISEASE OF THE PAROTID GLANDS

Polycystic (dysgenetic) disease is the least common of the benign cystic lesions of the parotid gland and is considered to be a developmental malformation of the duct system.

CLINICAL FEATURES

- High predilection in females.
- Usually evident during childhood and is bilateral in nature.
- Typical history is that of a recurrent painless swelling of the involved gland.

- No salivary or any other apparent abnormality of other salivary glands is evident.
- **Seifert et al, 1981**, reported that it has not been conclusively established whether polycystic (dysgenetic) disease of the parotid glands is associated with dysgenetic cyst of the kidney, liver, lung or pancreas.²⁶
- Although the multifocal cystic pattern seen in this lesion may suggest a differential diagnosis of mucoepidermoid carcinoma, acinic cell adenocarcinoma and cystadenocarcinoma, the histologic features of widespread involvement of salivary gland parenchyma, variable epithelial lining, presence of spheroliths and microliths and the relative lack of inflammation tilt the diagnosis in favor of polycystic (dysgenetic) disease of the parotid glands.
- Other viruses causing this infectious condition are cytomegalovirus, lymphocytic choriomeningitis virus, coxsackievirus A, echovirus and parainfluenza virus type C, etc.
- Acute suppurative sialadenitis is most commonly bacterial in origin.
- The causative agent most frequently implicated is *Staphylococcus aureus*. Other aerobic organisms isolated are *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Escherichia coli*. Anaerobic bacteria such as *Bacteroides* have been found to be involved as well. Stasis of saliva, often as a result of dehydration, is thought to be an integral component in the pathogenesis of this condition perhaps secondary to obstruction or decreased production.
- Decreased salivary flow with stasis is a key factor in chronic sialadenitis.
- Its development is often associated with a previous episode of acute suppurative inflammation with subsequent glandular destruction. Another possibility is recurrent parotitis of childhood which has continued into adulthood.

HISTOPATHOLOGIC FEATURES

- Architecture of the glands remains undisturbed; however, the lobules are markedly distended and nearly replaced by epithelium lined cysts, which impart a honey-combed or lattice-like appearance.
- Small residual islands of glandular acini are present between the cysts which vary in size and are variably lined by flattened, cuboidal or columnar epithelium. The columnar cells have abundant eosinophilic cytoplasm and rounded luminal borders. These features give the appearance of apocrine cells.
- Occasional ducts open directly into the cysts and some acinar units communicate with the cysts. These features suggest that the cysts arise from intercalated ducts.
- Most cyst lumina contain flocculent, eosinophilic material and a few scattered macrophages.
- Many cysts also contain spheroliths and microliths.

Management

No treatment is necessary, given the purely benign nature of this process.

SIALADENITIS

Sialadenitis, defined as inflammation of a salivary gland, is a common benign condition seen in children.

ETIOLOGY

- May arise from various etiological factors, which may either be infectious or non-infectious.
- Infectious sialadenitis may be of viral or bacterial origin.
- Mumps is the most common viral infection causing infectious sialadenitis. This illness is caused by an RNA virus from the paramyxovirus group.

CLINICAL FEATURES

- Infectious sialadenitis caused by paramyxovirus group (mumps) typically involves the parotid glands bilaterally.
- Children are most often affected.
- Occurs in the age group of four to six years.
- Transmission is via infected respiratory droplets.
- The parotid swelling is accompanied by constitutional symptoms such as fever and malaise and many cases are mild and subclinical in nature. Stenson's duct may be partially occluded.
- Onset of symptoms usually follows a two to three week incubation period and infection may be documented by a rise in convalescent serum titers to viral antigens or to isolation of the virus from the urine for a period from approximately one week prior and two weeks after.
- Serious sequelae are fortunately rare and often stem from involvement of other organ systems such as the CNS, pancreas and gonads.

HISTOPATHOLOGIC FEATURES (FIG. 11.4)

- Lesional area shows scattered infiltration of salivary gland parenchyma by lymphocytes and plasma cells.
- There is also acinar atrophy, ductal dilatation and fibrosis.

Management

1. Treatment is symptomatic in case of infectious sialadenitis of viral origin.
2. Complete bed rest is recommended.
3. Analgesics are prescribed.

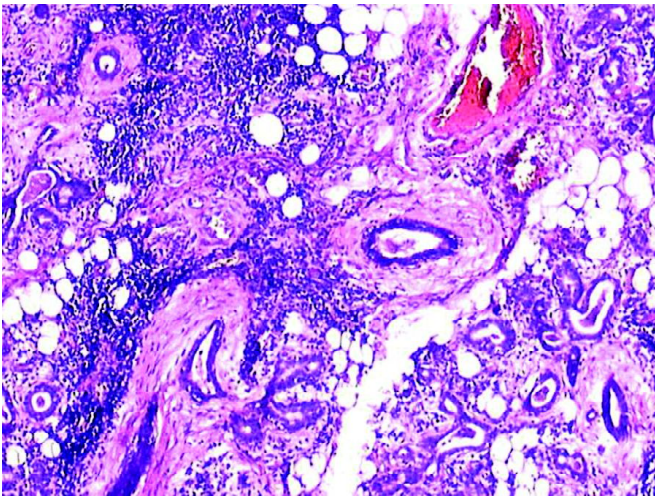


FIGURE 11.4: Histopathologic picture of chronic sialadenitis showing inflammation and fibrosis

4. In severe cases, corticosteroids are recommended for sialadenitis of viral origin.
5. Sialogogues, heat, massage of the affected gland and the administration of an appropriate intravenous antibiotic, usually a penicillinase-resistant anti-staphylococcal antibiotic are preferred treatment modalities for sialadenitis of bacterial origin.
6. Improvement is expected within the first 24 to 48 hours. If this does not occur, operative intervention may be indicated. This usually consists of a standard parotidectomy—skin incision and flap followed by creation of several openings within the substance of the gland parallel to the course of the facial nerve. A drain is then placed over the gland and the wound closed.

SARCOIDOSIS (FIG. 11.5)

Sarcoidosis takes its name from the Greek words, *sarx*, meaning “flesh” and *osis*, meaning “condition.” Hence, sarcoidosis is nothing but a flesh (skin) condition. Sarcoidosis is a granulomatous disease of unknown etiology which might affect many systems.²⁷ Although the disease is generally encountered between 20 to 40 years of age, it might be seen at any age.²⁸ A few cases of sarcoidosis in children have been reported by *Siltzbach and Greenberg, 1968*²⁹ and *Jasper and Denny, 1968*.³⁰

ETIOLOGY

- Unknown.
- Molecular biologic techniques suggest a possible role of *mycobacterium tuberculosis* or a related organism as a causative agent.



FIGURE 11.5: Sarcoidosis showing symmetric infiltrative violaceous plaques on both the eyelids

CLINICAL FEATURES

- Occurs at any age, most common in second to fourth decade.
- Pulmonary manifestations are most characteristic of this disease.
- Parotid swelling occurs either unilaterally or bilaterally.
- Skin lesions occur in approximately 25 percent of the cases in the form of erythema nodosum and symmetric infiltrative violaceous plaques on the nose, cheeks, ears, forehead and hands; a term known as ‘*lupus perino*’.
- Ocular involvement is variable.
- Hepatic involvement occurs in 60 percent of cases.
- Osseous lesions are mostly seen in 5 percent of cases.
- Granulomas may occur in nasal sinuses, pharynx, epiglottis and larynx.

DIAGNOSIS

Kveim test was widely used earlier, but has largely been replaced by detection in serum of the levels of calcium, angiotensin I converting enzyme (ACE), lysozyme and adenosine deaminase in recent times.

HISTOPATHOLOGIC FEATURES (FIG. 11.6)

- Histopathologically, non-caseating granulomas consisting of epithelioid macrophages and multinucleated giant cells are seen.
- These granulomas may contain stellate inclusions (asteroid bodies) and concentrically laminar calcifications (Schaumann bodies).
- Periphery of the lesion shows diffuse lymphocytic infiltrate.

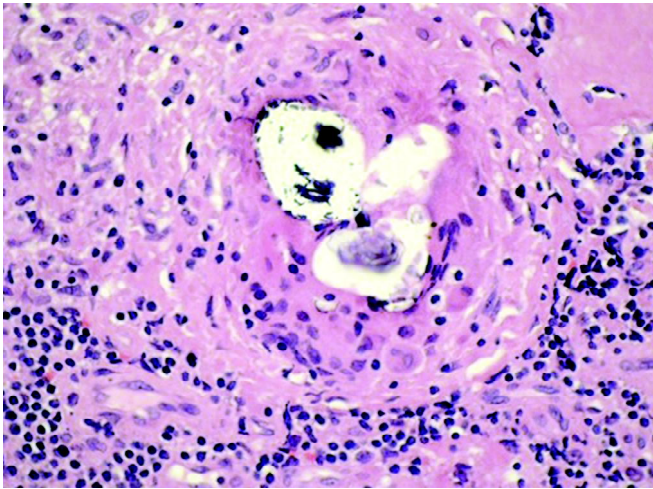


FIGURE 11.6: Histopathologic picture of sarcoidosis showing central area of calcification (Schaumann bodies), surrounded peripherally by diffuse lymphocytic infiltrate

Management

1. Corticosteroids seem to be the drug of choice in treating symptomatic pulmonary sarcoidosis.
2. Chloroquine, either alone or in combination with corticosteroids may appear beneficial.
3. Immunosuppressive drugs may be used for patients not responding to steroid treatment.

SIALOLITHIASIS

It is estimated that sialolithiasis affects 12 in 1000 of the adult population but is not very frequently seen in the pediatric population.³¹ Sialolithiasis accounts for more than 50 percent of diseases of the large salivary glands and is thus the most common cause of acute and chronic infections.³²

ETIOLOGY

- The exact etiology and pathogenesis of salivary calculi is largely unknown.
- Genesis of calculi lies in the relative stagnation of calcium rich saliva. They are thought to occur as a result of deposition of calcium salts around an initial organic nidus consisting of altered salivary mucins, bacteria and desquamated epithelial cells.³³
- For stone formation it is likely that intermittent stasis produces a change in the mucoid element of saliva, which forms a gel. This gel produces the framework for deposition of salts and organic substances creating a stone.
- Traditional theories suggest that the formation occurs in two phases: a central core and a layered periphery.³⁴
- The central core is formed by the precipitation of salts, which are bound by certain organic substances. The second

phase consists of the layered deposition of organic and inorganic material.

- Submandibular stones are thought to form around a nidus of mucous, whereas parotid stones are thought to form most often around a nidus of inflammatory cells or a foreign body.
- Another theory that has been proposed states that an unknown metabolic phenomenon can increase the salivary bicarbonate content, which alters calcium phosphate solubility and leads to precipitation of calcium and phosphate ions.³⁵
- A retrograde theory for sialolithiasis has also been proposed. Some substances or bacteria within the oral cavity might migrate into the salivary ducts and become the nidus for further calcification. A case in which stone formation around a vegetal nidus was histologically proven has been reported. Salivary stagnation, increased alkalinity of saliva, infection or inflammation of the salivary duct or gland, and physical trauma to salivary duct or gland may predispose to calculus formation.
- Submandibular sialolithiasis is more common as its saliva is (i) more alkaline, (ii) has an increased concentration of calcium and phosphate, and (iii) has a higher mucous content than saliva of the parotid and sublingual glands. In addition, the submandibular duct is longer and the gland has an antigravity flow. Stone formation is not associated with systemic abnormalities of calcium metabolism. Electrolyte and parathyroid hormone studies in patients with sialolithiasis have not shown any significant abnormalities.³⁶

CLINICAL FEATURES

- Males are affected twice as much as females.
- Children are rarely affected but a review of the literature reveals 100 cases of submandibular calculi in children aged 3 weeks to 15 years.³⁷
- More than 80 percent occur in the submandibular gland or its duct, 6 percent in the parotid gland and 2 percent in the sublingual gland or minor salivary glands.
- Salivary calculi are usually unilateral and are not a cause of dry mouth.³⁸
- Clinically they are round or ovoid, rough or smooth and of a yellowish color (Fig. 11.7). They consist mainly of calcium phosphate with small amounts of carbonates in the form of hydroxyapatite and smaller amounts of magnesium, potassium and ammonia. This mix is distributed evenly throughout.³⁹
- Submandibular stones are 82 percent inorganic and 18 percent organic material whereas parotid stones are composed of 49 percent inorganic and 51 percent organic material. The organic material is composed of various carbohydrates and amino acids. Bacterial elements have not been identified at the core of a sialolith.



FIGURE 11.7: Salivary duct stone

- Sialolithiasis typically causes pain and swelling of the involved salivary gland by obstructing the food related surge of salivary secretion. Calculi may cause stasis of saliva, leading to bacterial ascent into the parenchyma of the gland and therefore infection, pain and swelling of the gland.
- Some may be asymptomatic until the stone passes forward and can be palpated in the duct or seen at the duct orifice. It may be possible that obstruction caused by large calculi is sometimes asymptomatic as obstruction is not complete and some saliva manages to seep through or around the calculus.
- Long term obstruction in the absence of infection can lead to atrophy of the gland with resultant lack of secretory function and ultimately fibrosis.

Recently, **Chung et al, 2007** in their study differentiated between pediatric and adult sialolithiasis in a total of 210 patients with sialolithiasis confirmed by surgical treatment. Twenty-nine of the 210 patients were of pediatric age group (age $\leq$ 18 years) and 181 were adult patients (age $>$ 19 years). Comparison of pediatric and adult sialolithiasis was performed in terms of subject characteristics, clinical manifestations, salivary calculi characteristics, treatment modalities and outcomes. They reported that postprandial recurrent swelling was the most frequent complaint in pediatric sialolithiasis patients, similar to that in adult patients. However, duration of symptoms was shorter in pediatric patients (mean 14.1 months versus 30.7 months in adults). Most calculi were less than 1cm in pediatric patients (93.1 percent), compared to 56.3 percent of the adult patients. The calculi were located more in the distal duct (62.0 percent) than in proximal duct and gland in the pediatric patients, whereas 44.7 percent were present in the distal duct in adult patients.⁴⁰

DIAGNOSIS

- Careful history and examination are important in the diagnosis of sialolithiasis. Pain and swelling of the concerned gland at mealtimes and in response to other salivary stimuli are especially important. Complete obstruction causes constant pain and swelling, pus may be seen draining from the duct and signs of systemic infection may be present.
- Bimanual palpation of the floor of the mouth, in a posterior to anterior direction, reveals a palpable stone in a large number of cases of submandibular calculi formation. Bimanual palpation of the gland itself can be useful, as a uniformly firm and hard gland suggests a hypo-functional or non-functional gland. Recently Chung et al, 2007, in their study reported that because of large proportion of relatively small and distal sialolithiasis in pediatric patients, careful bimanual palpation of the oral cavity is mandatory in the diagnostic approach for children suspicious of sialolithiasis.⁴⁰
- For parotid stones, careful intraoral palpation around Stenson's duct orifice may reveal a stone. Deeper parotid stones are often not palpable.
- When minor salivary glands are involved they are usually in the buccal mucosa or upper lip, forming a firm nodule that may mimic a tumor.
- Imaging studies are very useful for diagnosing sialolithiasis. Occlusal radiographs are useful in showing radiopaque stones (Fig. 11.8). It is very uncommon for patients to have a combination of radiopaque and radiolucent stones;



FIGURE 11.8: Occlusal radiograph showing radiopaque salivary duct stone

40 percent of parotid stones may be radiolucent. Sialography is thus useful in patients showing signs of sialadenitis related to radiolucent stones or deep submandibular/parotid stones. Sialography is, however, contraindicated in acute infection or in significant patient contrast medium allergy.

Management

1. Patients presenting with sialolithiasis may benefit from a trial of conservative management, especially if the stone is small. The patient must be well hydrated and the clinician must apply moist warm heat and gland massage, while sialogogues are used to promote saliva production and flush the stone out of the duct. With swelling of the gland and sialolithiasis, infection should be assumed and a penicillinase resistant anti-staphylococcal antibiotic prescribed. Most stones will respond to such a regimen, combined with simple sialolithotomy when required.⁴¹
2. Almost half of the submandibular calculi lie in the distal third of the duct and are amenable to simple surgical release through an incision in the floor of the mouth, which is relatively simple to perform and not usually associated with complications.⁴² Recently, Chung et al, 2007, in their study have also suggested that intra-oral approach is an effective treatment procedure for most of the cases of sialolithiasis in children.⁴⁰
3. If the stone is sufficiently forward it can be milked and manipulated through the duct orifice. This can be done with the aid of lacrimal probes and dilators to open the duct. Once open, the stone can be identified, milked forward, grasped and removed. The gland is then milked to remove any other debris in the more posterior portion of the duct.
4. The duct may need opening to retrieve the stone. This involves a transoral approach where an incision is made directly onto the stone. In this way more posterior stones, 1 to 2 cm from the punctum, can be removed by cutting directly onto the stone in the longitudinal axis of the duct. Care is taken as the lingual nerve lies deep, but in close association with the submandibular duct posteriorly. Subsequently, the stone can be grasped and removed. No closure is done leaving the duct open for drainage.
5. If the gland has been damaged by recurrent infection and fibrosis, or calculi have formed within the gland, it may require removal.
6. Parotid stone management is more problematic as only a small segment of Stenson's duct is approachable through an intraoral incision. In addition, opening Stenson's duct can be complicated by subsequent stenosis of the duct whereas this is rare in the submandibular gland. As a result, parotidectomy is the mainstay of surgical management for the majority of intraglandular stones. This is reserved for patients whose symptoms do not respond to conservative therapy and suffer from recurrent pain and swelling.
7. Alternative methods of treatment have emerged such as the use of extracorporeal shock wave lithotripsy (ESWL) and more recently the use of endoscopic intracorporeal shockwave lithotripsy (EISWL), in which shockwaves are delivered directly to the surface of the stone lodged within the duct without damaging adjacent tissue (piezoelectric principle). Both extra and intracorporeal lithotripsy is gaining increasing importance in the treatment of salivary stone disease.³²
8. In extracorporeal piezoelectric lithotripsy, the average size of fragments produced is about 0.7 mm. Duct diameters are greater than 0.7 mm in general except for at the ostium. Therefore, fragments produced by ESWL would not be prohibited by duct diameters. Findings have also suggested that best results in salivary stone lithotripsy are achieved when the maximum size of stone fragments does not exceed 1.2 mm.⁴³
9. Extracorporeal salivary lithotripsy provides another therapeutic option that carries fewer risks than surgical removal of the affected gland, such as the risks of a general anesthetic administration, facial nerve damage, surgical scar, Frey's syndrome and causes little discomfort to the patient whilst preserving the gland.⁴⁴
10. A retrospective study of patients treated endoscopically from 1994 to 1999 showed a success rate of 83 percent with no severe complications.⁴⁵
11. Endoscopy is a minimally invasive technique for removal of calculi from salivary glands as well as an excellent diagnostic procedure, as miniaturised endoscopes conforming to the physiological widths of the ducts are used to directly view and then deliver shock waves to the stones.⁴⁶

BENIGN NEOPLASMS

PLEOMORPHIC ADENOMA

It is a mixed tumor which shows epithelial and connective tissue features. Major and minor salivary glands are most commonly involved. Pleomorphic adenoma was believed to originate from cells of more than one germ layer hence was variously termed as branchioma, enclavoma etc. WHO termed it as pleomorphic adenoma because of a varied appearance under microscopic field. The term "Pleomorphic" was first suggested by Willis, 1948.⁴⁷ It is usually more common in the 4th to 6th decades, hence not discussed in detail.

WARTHIN'S TUMOR

1st described by Hildebrand in 1895⁴⁸ as congenital cyst of the neck. Warthin in 1929⁴⁹ termed it as "papillary cystadenoma

lymphomatosum”. Also called as cystic papillary adenoma, branchiogenic adenoma, branchial cysts of parotid. It has rarely been reported in the pediatric age group. The literature shows its incidence as less than one percent of all salivary gland neoplasms in children. This warrants only a brief description of the tumor.

MALIGNANT NEOPLASMS

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma is the most common salivary gland malignancy. It comprises of 5 to 9 percent of salivary neoplasms. De and Tribedi, 1939 first described mixed epidermoid and mucous secreting carcinoma of parotid.⁵⁰ Stewart, Foot and Becker, 1945, gave the term “Mucoepidermoid carcinoma.”⁵¹

CLINICAL FEATURES

- Age: 3rd to 8th decades, peak in 5th decade
- Slight female predilection is seen
- Most common salivary gland malignancy of children
- Five to nine percent of salivary neoplasms
- Site: Parotid-45-70 percent of cases, palate - 18 percent of cases
- More often seen in Caucasian than African American population
- Presents as low grade and high grade tumors
- Low-grade: Slow growing, painless mass
- High-grade: Rapidly enlarging, pain may or may not be present
- In minor salivary glands it may be mistaken for benign or inflammatory process such as:
 - Hemangioma
 - Papilloma
 - Tori.

CLINICAL STAGING

American Joint Committee in 1988 proposed the staging criteria based on four clinical variables viz; tumor size, local extension of tumor, the palpability of and suspected metastasis to regional lymph nodes and the presence or absence of distant metastasis.

Primary tumor (T)

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

T1: Tumor 2 cm or less in greatest diameter.

T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension.

T3: Tumor more than 4 cm but not more than 6 cm in greatest dimension.

T4: Tumor more than 6 cm in greatest dimension.

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.

N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.

N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.

N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N3: Metastasis in lymph node more than 6 cm in greatest dimension.

Distant metastasis (M)

MX: Presence of distant metastasis cannot be assessed.

M0: No distant metastasis.

M1: Distant metastasis.

Stage grouping

Stage 1:	T1a	N0	M0
	T2a	N0	M0
Stage 2:	T1b	N0	M0
	T1b	N0	M0
Stage 3:	T3b	N0	M0
	T4a	N0	M0
Any T (except T4b)		N1	M0
Stage 4:	T4b	Any N	M0
	Any T	N2N3	M0
	Any T	Any N	M1

GROSS PATHOLOGY

- Well-circumscribed to partially encapsulated to unencapsulated mass.
- Solid tumor with cystic spaces.

HISTOPATHOLOGIC FEATURES

Grading criteria

- Grading criteria are based on:
 - Degree of cyst formation as opposed to solid growth.
 - Proportion of cell types.
 - Presence or absence of cytomorphologic atypia.
- Divided into three types:
 1. Low grade.
 2. Intermediate grade.
 3. High grade.

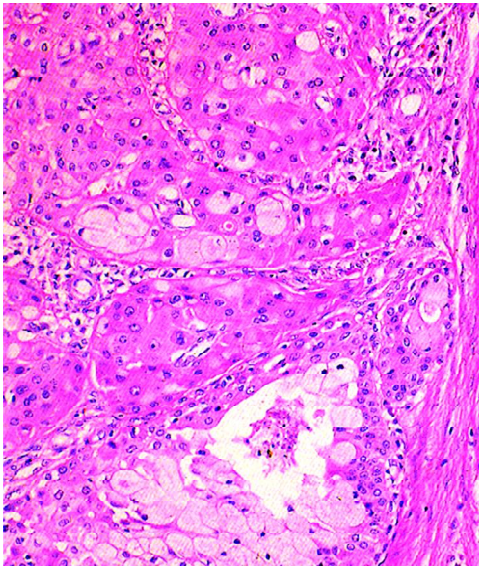


FIGURE 11.9: Histopathologic picture of low grade mucoepidermoid carcinoma showing mucous cells predominating epidermoid cells

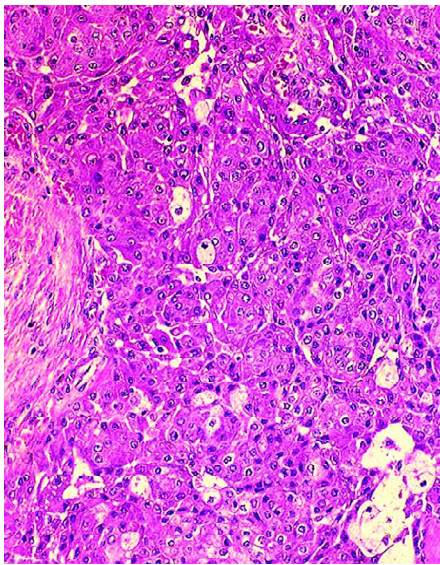


FIGURE 11.10: Histopathologic picture of intermediate grade mucoepidermoid carcinoma showing increased cellular pleomorphism in epidermoid cells

- Low-grade tumor (Fig. 11.9):
 - Mucus cells predominate epidermoid cells.
 - Prominent cysts.
 - Mature cellular elements.
- Intermediate- grade tumor (Fig. 11.10):
 - Mucus and epidermoid cells are equal in number.

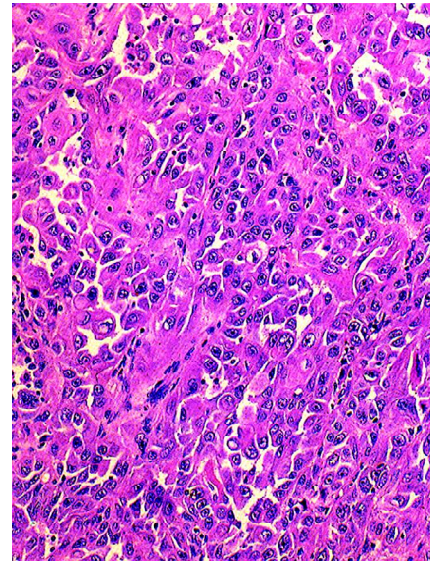


FIGURE 11.11: Histopathologic picture of high grade mucoepidermoid carcinoma showing predominant epidermoid cells with increased mitotic figures and cellular pleomorphism

- Fewer and smaller cysts.
- Increasing pleomorphism and mitotic figures
- High-grade tumor (Fig. 11.11):
 - Epidermoid cells predominate mucus cells.
 - Solid tumor cell proliferation.
 - Cytologic pleomorphism.
 - Numerous mitotic figures.
 - May be mistaken for squamous cell carcinoma.

Management

1. Conservative surgical approach with preservation of facial nerve for stage I and stage II mucoepidermoid carcinomas.
2. Aggressive surgical approach for stage III and stage IV mucoepidermoid carcinomas.
3. Radical neck dissection performed in patients with cervical node metastasis.
4. For minor salivary gland mucoepidermoid carcinomas, treatment is primarily surgical.
5. In case if bone is not involved, wide excision down to periosteum with 1 or 2 cm tumor free lateral margins is recommended.
6. Use of radiotherapy is controversial as most of the researchers think that these lesions are radioresistant. Also, radiotherapy is contraindicated as it may give rise to other neoplasms such as sarcomas.
7. **Kaplan et al**⁵² and **Suen and Johns**⁵³ have suggested that high grade mucoepidermoid carcinoma may show similarity to squamous cell carcinoma.

ACINIC CELL ADENOCARCINOMA

Acinic cell adenocarcinoma is the second most common parotid and pediatric malignancy.

CLINICAL FEATURES

- Most common in the 5th decade
- Female predilection is seen
- Bilateral parotid disease is seen in three percent of the cases
- Solitary, slow-growing, often painless mass.

GROSS PATHOLOGY

- Well-demarcated tumor mass.
- Most often homogeneous.

HISTOPATHOLOGIC FEATURES

- Polyhedral cells.
- Small, dark, eccentric nuclei.
- Basophilic granular cytoplasm.

Four growth patterns may be seen:

- Solid
- Microcystic
- Papillary cystic
- Follicular.

Solid growth pattern

- Large number of well-differentiated acinar cells mostly resembling normal parotid gland parenchyma.
- Absence of striated ducts distinguish a solid growth from normal salivary gland parenchyma.

Microcystic (Fig. 11.12)

- More commonly seen growth pattern
- Small cystic spaces are seen
- Well-differentiated acinar cells, vacuolated and intercalated duct-like cells
- Microcystic space is due to coalescence of intracellular vacuoles of ruptured cells.

Papillary cystic

- One or more cystic structures that contain proliferation of epithelium
- Few folds of lining epithelium projecting into the lumina may be seen.

Follicular

- Least frequently encountered growth type
- Round cystic spaces lined by cuboidal or low columnar epithelial cells
- Intercystic space contains non-specific glandular cells with some vacuolated and acinic type of cells.

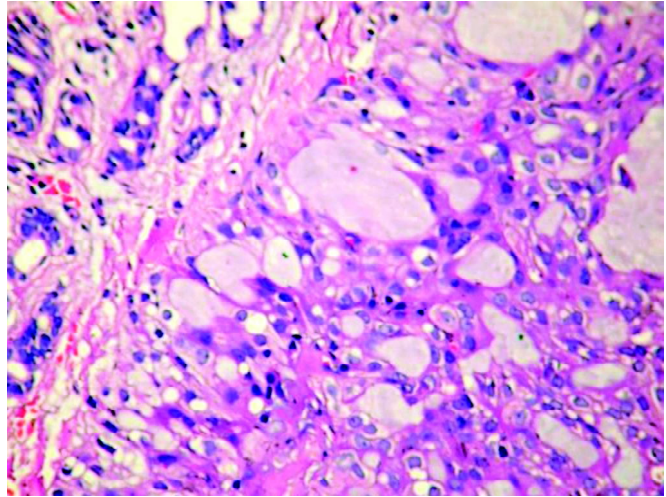


FIGURE 11.12: Histopathologic picture of acinic cell adenocarcinoma showing microcystic growth pattern

Management

1. Surgical excision is the treatment of choice.
2. If the tumor is confined to the superficial lobe of the parotid gland, superficial parotidectomy is performed.
3. When deep lobe is involved, total parotidectomy is performed.
4. Local enucleation is avoided.
5. In case of involvement of submandibular gland, total resection of the gland is done.
6. In case of involvement of minor salivary glands, complete local excision is required.
7. Radical neck dissection is done only in cases of cervical lymph node involvement.

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Skin Lesions in Children

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CHAPTER OVERVIEW

Introduction
Ectodermal dysplasia
Dyskeratosis congenita
Incontinentia pigmenti
Pachyonychia congenita
Ehlers-Danlos syndrome
Osler-Weber-Rendu syndrome
Peutz-Jeghers syndrome

White sponge nevus
Epidermolysis bullosa
Pemphigus:
Pemphigus foliaceus
Pemphigus vegetans
Pemphigus erythematosus
Paraneoplastic pemphigus
IgA pemphigus

INTRODUCTION

Skin is the soft and pliant membrane which covers the entire surface of the body. It is man's front-line protective barrier between internal structures and the external environment. It is tough, resilient, and virtually impermeable to aqueous solutions, bacteria, or toxic compounds. It protects against trauma, regulates body temperature, serves as an organ of excretion and sensation, and synthesizes vitamin D in the presence of ultraviolet light. It has three primary layers: epidermis, dermis, and subcutaneous tissue. The epidermis (the outermost layer) produces keratin as its primary function. The epidermis contains two sublayers: the stratum corneum, an outer horny layer of keratin that protects the body against harmful environmental substances and restricts water loss, and the cellular stratum, where keratin cells are synthesized. The basement membrane lies beneath the cellular stratum and serves to attach the epidermis to the dermis. The dermis, the second primary layer of the skin, consists of two fibrous proteins, fibroblasts, and an intervening ground substance. The proteins are collagen, which strengthens the skin to prevent it from tearing, and elastin to give it resilience. The ground substance, which makes the skin soft and compressible, contains primarily dermis (top layer) and the reticular dermis (bottom layer). Subcutaneous tissue, the third primary layer of the skin, consists mainly of fat (containing mostly triglycerides), which provides heat

insulation, shock absorption, and a reserve of calories. Both sensory and motor nerves (autonomic fibers) are found in the dermis and the subcutaneous tissue.

Any abnormality within the structure or function of the various layers of skin, may be genetic or environmental, may lead to skin diseases or disorders. The diseases of the skin are divided into: Inflammation of the skin; Enlargement of the papillae of the skin; Disorders of the vessels of the skin; Disorders of the sensibility of the skin; Disorders of the color producing function of the skin.

ECTODERMAL DYSPLASIA

The ectodermal dysplasias (EDs) comprise a large, heterogeneous group of inherited disorders that are defined by primary defects in the development of two or more tissues derived from embryonic ectoderm. The tissues primarily involved are the skin, hair, nails, eccrine glands and teeth. Although *Thurnam*¹ published the first report of a patient with ectodermal dysplasia in 1848, the term ectodermal dysplasia was not coined until 1929 by Weech.²

CLASSIFICATION

Freire-Maia and Pinheiro proposed the first classification system of the ectodermal dysplasias in 1982.³ Their original

classification system stratified the ectodermal dysplasias into different subgroups according to the presence or absence of:

1. Hair anomalies or trichodysplasias
2. Dental abnormalities
3. Nail abnormalities or onychodysplasias, and
4. Eccrine gland dysfunction or dyhidrosis.

Priolo and Laganà, 2001,⁴ reclassified the ectodermal dysplasias into two main functional groups: (1) Defects in developmental regulation/epithelial-mesenchymal interaction; and (2) Defects in cytoskeleton maintenance and cell stability. **Lamartine**⁵ reclassified the ectodermal dysplasias into the following four functional groups based on the underlying pathophysiologic defect: (1) Cell-to-cell communication and signaling; (2) Adhesion; (3) Development; and (4) Others. Other classification systems categorize the ectodermal dysplasias based on defects in cell-cell communication and signaling, adhesion, transcription regulation, or development.⁶

ETIOLOGY

Various genes responsible for signs and symptoms of ED have been found such as:

- Keratitis, ichthyosis, deafness (KID) syndrome is caused by mutations in the GJB2 gene, which encodes connexin 26.
- Margarita Island ectodermal dysplasia is caused by mutations in the PVRL1 gene, which encodes nectin-1.
- Ectodermal dysplasia with skin fragility is caused by mutations in the PKP1 gene, which encodes plakophilin 1.

CLINICAL FEATURES

- X-linked recessive hypohidrotic ectodermal dysplasia has full expression only in males. Female carriers outnumber affected men, but females show little or no signs of the condition. Carriers always outnumber live affected patients because of spontaneous abortion of the highly affected fetuses.
- Many patients are not diagnosed until infancy or childhood, when dental anomalies, nail abnormalities or alopecia become apparent.
- Dry, hypopigmented skin is a feature. A chronic eczematous dermatitis may be present.
- Sweating may be absent or reduced.
- Sparse, fair, brittle hair with alopecia is a feature, as are absent or diminished body hair and sparse or absent eyebrows and eyelashes.
- Nail dystrophy is a feature.
- Dental features may include hypodontia or anodontia; malformed, rudimentary, or pegged teeth; and/or enamel defects and frequent dental caries.
- Diminished lacrimation and salivation are reported.
- Dysmorphic facies is a feature.

- X-linked hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome) is the most common ectodermal dysplasia. The patients suffering from this condition show the following features:
 - The typical facies, which is often not recognized until infancy, is characterized by frontal bossing, sunken cheeks, saddle nose, thick and everted lips, wrinkled, hyperpigmented periorbital skin and large, low-set ears (Fig. 12.1).
 - Dental manifestations include conical or pegged teeth, hypodontia or complete anodontia and delayed eruption of permanent teeth (Fig. 12.2).
 - Most patients have fine, sparse, lusterless, fair hair (Fig. 12.3).
 - Onychodystrophy may occur but is not common.
 - Extensive scaling of the skin and unexplained pyrexia secondary to anhidrosis may occur in the neonatal period. The development of a chronic eczematous dermatitis is common.
 - Other common signs are short stature, eye abnormalities, decreased tear secretions and photophobia.
- Hidrotic ectodermal dysplasia (Clouston syndrome) is inherited in an autosomal dominant manner; the homozygous state may be lethal. The patients suffering from this condition show the following features:
 - Scalp hair is very sparse, fine, and brittle and alopecia is common. Eyebrows are thinned or absent.
 - Nail dystrophy is common. Persistent paronychia infections are frequent. Polydactyly, syndactyly and bulbous fingertips may be present.
 - Patients have normal facies, no specific dental defects and normal sweating.



FIGURE 12.1: Ten-year-old child with ectodermal dysplasia showing hyperpigmented periorbital skin, thick, everted lips due to decreased vertical height of the jaws, depressed nasal bridge and saddle nose



FIGURE 12.2: Three-year-old child with ectodermal dysplasia showing peg shaped incisors



FIGURE 12.3: Three-year-old child with ectodermal dysplasia showing sparse hair

- Other reported findings include reticulate hyperpigmentation of the knees, elbows, and fingers; palmoplantar keratoderma; and eccrine poromatosis.
- Hay-Wells syndrome is inherited as an autosomal dominant trait of variable expressivity. The patients suffering from this condition show the following features:⁷
 - Scaling and erythema may be present at birth. The characteristic facies is due to ankyloblepharon (congenital adhesion of the upper and lower eyelid margins by fibrous bands); a broad nasal bridge; and a sunken, hypoplastic maxilla. Cleft palate is common; cleft lip is rare.
 - Recalcitrant, crusted, inflammatory scalp dermatitis may cause scarring alopecia. Chronic blepharitis and

conjunctivitis may develop. Nails are absent or dystrophic; pegged teeth are common. Mild hypohidrosis is common. Hair may be sparse and coarse.

- Ectodactyly-Ectodermal dysplasia-Cleft syndrome (EEC) syndrome is inherited as an autosomal dominant trait of low penetrance and variable expressivity. Many sporadic cases have been reported. Ectrodactyly with tetramelic 3 to 4 syndactyly results in the characteristic lobster-claw deformity of the hands and feet. Hypoplastic metacarpal or metatarsal bones may be present. Cleft lip and palate create a characteristic nasal contour.
 - Other ectodermal anomalies include mild hypohidrosis, coarse, dry hair with hypotrichosis, xerostomia, dystrophic nails, dental enamel hypoplasia and microdontia.
 - Associated defects include blepharophimosis, lacrimal duct anomalies, strabismus, deafness, choanal atresia and abnormalities of the genitourinary tract.
- Rapp-Hodgkin ectodermal dysplasia is an autosomal dominant syndrome. Felding noted that high forehead, narrow nose, cleft lip or palate, and maxillary hyperplasia produce a distinctive facies.⁸ Hypohidrosis is severe enough to result in heat intolerance. Dental defects include conical teeth and hypodontia. Hair are sparse, has a steel-wool texture, and may show pili torti or pili canaliculi. Many patients present with recalcitrant, inflammatory scalp dermatitis followed by scarring alopecia. Nails are narrow and dystrophic. Occasional abnormalities include deafness, eye defects, and hypospadias.

HISTOPATHOLOGIC FEATURES

- Lesional area shows decrease in number of sweat glands, hair follicles and sebaceous glands.
- Adnexal structures present are hypoplastic.
- Epidermis is thin and flattened.

Management

1. For patients with anhidrosis / hypohidrosis, encourage frequent consumption of cool liquids to maintain adequate hydration and thermoregulation.
2. Dhanrajani PJ recommends that for patients with dental defects, early dental evaluation and intervention and routine dental hygiene be performed. Dentures may be indicated as early as age two years. Multiple replacements may be needed as the child grows, and dental implants may eventually be required. Advise orthodontic treatment for cosmetic reasons and to ensure adequate nutritional intake.⁹
3. Patients with xerosis or eczematous dermatitis may benefit from the use of topical emollients.
4. Patients with scalp erosions should be treated with topical and systemic antibiotics as needed. General

scalp care may involve the use of weekly dilute bleach baths or acetic acid soaks to minimize bacterial colonization of the scalp. Application of special scalp dressings may be helpful.

5. Use artificial tears to prevent damage to the cornea in patients with reduced lacrimation.
6. Protect nasal mucosa with saline sprays followed by the application of petrolatum.
7. Patients with ectodermal dysplasia with immunodeficiency should be monitored for infection and treated with therapeutic and/or prophylactic antibiotics when appropriate.
8. Dupuis-Girod S et al report that allogeneic stem cell transplantation has been performed in a small number of patients with autosomal dominant ectodermal dysplasia with immunodeficiency (EDA-ID); poor engraftment and post-transplant complications were common.¹⁰
9. Other midfacial defects or hand/foot deformities may be surgically corrected in order to improve function and reduce physical disfigurement.

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DKC), also known as **Zinsser-Engman-Cole syndrome**, is a rare, progressive bone marrow failure syndrome characterized by the triad of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia. Mutations in DKC1 have been shown to cause the X-linked form of DKC. The inheritance pattern of most cases of DKC is X-linked recessive, but autosomal dominant and recessive patterns have been reported. Autosomal dominant DKC is associated with TERC and TERT mutations in some cases, and NOP10 has been associated with some cases of autosomal recessive DKC.¹¹

CLINICAL FEATURES

- The primary finding is abnormal skin pigmentation, with tan-to-gray hyperpigmented or hypopigmented macules and patches in a mottled or reticulated pattern. Reticulated pigmentation occurs in approximately 90 percent of patients. Poikilodermatous changes with atrophy and telangiectasia are common.
- The cutaneous presentation may clinically and histologically resemble graft versus host disease. The typical distribution involves the sun-exposed areas, including the upper trunk, neck and face.
- Other cutaneous findings may include alopecia of the scalp, eyebrows, and eyelashes; premature graying of the hair; hyperhidrosis; hyperkeratosis of the palms and soles; and adermatoglyphia (loss of dermal ridges on fingers and toes).
- Nail dystrophy is seen in approximately 90 percent of patients, with fingernail involvement often preceding toenail involvement (Fig. 12.4).

- Progressive nail dystrophy begins with ridging and longitudinal splitting. Progressive atrophy, thinning, pterygium, and distortion eventuate in small, rudimentary, or absent nails.
- Mucosal leukoplakia occurs in approximately 80 percent of patients and typically involves the buccal mucosa, tongue (Fig. 12.5), and oropharynx. The leukoplakia may become verrucous, and ulceration may occur. Patients also may have an increased prevalence and severity of periodontal disease.



FIGURE 12.4: Dyskeratosis congenita showing dystrophic nail beds



FIGURE 12.5: Dyskeratosis congenita showing hyperkeratosis of dorsal tongue mucosa

- Other mucosal sites may be involved (e.g. esophagus, urethral meatus, glans penis, lacrimal duct, conjunctiva, vagina, anus). Constriction and stenosis can occur at these sites, with subsequent development of dysphagia, dysuria, phimosis, and epiphora.
- Approximately 90 percent have peripheral cytopenia of one or more lineages. In some cases, this is the initial presentation, with a median age of onset of 10 years.
- Bone marrow failure is a major cause of death, with approximately 70 percent of deaths related to bleeding and opportunistic infections as a result of bone marrow failure.
- Approximately 20 percent of individuals with DKC develop pulmonary complications, including pulmonary fibrosis and abnormalities of pulmonary vasculature.
- The recommendation is that DKC patients avoid taking drugs with pulmonary toxicity (e.g. busulfan) and that they have their lungs shielded from radiation during bone marrow transplant (BMT).
- Patients have an increased prevalence of malignant mucosal neoplasms, particularly squamous cell carcinoma of the mouth, nasopharynx, esophagus, rectum, vagina, or cervix. These often occur within sites of leukoplakia.
- The prevalence of squamous cell carcinoma of the skin is also increased. Other malignancies reported include Hodgkin's lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma.
- Malignancy tends to develop in the third decade of life.
- Patients may have learning difficulties and mental retardation.
- Dyskeratosis congenita reportedly is associated with conjunctivitis, blepharitis, and pterygium. Lacrimal duct stenosis resulting in epiphora (i.e. excessive tearing) occurs in approximately 80 percent of patients.
- Patients may have mandibular hypoplasia, osteoporosis, avascular necrosis, and scoliosis.
- Gastrointestinal system findings: These may include esophageal webs, hepatosplenomegaly, and cirrhosis.
- Hypospastic testes, hypospadias, and ureteral stenosis have also been reported.

HISTOPATHOLOGIC FEATURES (FIG. 12.6)

- Lesional area in dyskeratosis congenita shows atrophic epidermis with areas of hyperpigmentation in the basal layer, and melanophages, telangiectasia, and mild infiltration of inflammatory cells in the superficial dermis.
- Blister beneath the epidermis is evident due to liquefaction degeneration of the basal cells.

Management

1. Symptomatic treatment.
2. Routine medical examination to rule out development of aplastic anemia.

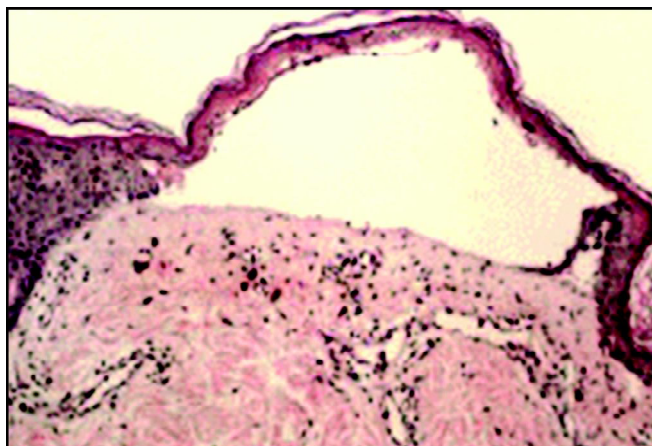


FIGURE 12.6: Histopathologic picture of dyskeratosis congenita showing atrophic epidermis with areas of hyperpigmentation in the basal layer, and melanophages, telangiectasia, and mild infiltration of inflammatory cells in the superficial dermis. Blister beneath the epidermis is due to liquefaction and degeneration of the basal cells



FIGURE 12.7: Incontinentia pigmenti showing macular brown lesions on the skin of limb

3. Short-term treatment options for bone marrow failure in patients with DKC include anabolic steroids (e.g.: oxymetholone), granulocyte macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and erythropoietin.¹²
4. The only long-term, curative option is hematopoietic stem cell transplantation (SCT).

INCONTINENTIA PIGMENTI (FIG. 12.7)

Incontinentia pigmenti (IP) is an X-linked dominant neuro-cutaneous syndrome with cutaneous, neurologic, ophthalmologic, and dental manifestations. **Garrod** reported the first probable case of incontinentia pigmenti in 1906 and described it as a peculiar pigmentation of the skin in an infant.¹³

ETIOLOGY

Incontinentia pigmenti is caused by mutations in the NEMO/IKK- γ gene, which is located on chromosome Xq28.

CLINICAL FEATURES

Incontinentia pigmenti is an X-linked dominant, male lethal syndrome. More than 95 percent of reported cases of incontinentia pigmenti occur in females.

The proposed diagnostic criteria for incontinentia pigmenti are as follows:

In the absence of a family history, the presence of at least one major criterion is necessary. The presence of minor criteria supports the diagnosis of incontinentia pigmenti.

- Major criteria
 - Typical neonatal vesicular rash with eosinophilia
 - Typical blaschkoid hyperpigmentation on the trunk, fading in adolescence
 - Linear, atrophic hairless lesions.
- Minor criteria
 - Dental anomalies
 - Alopecia
 - Woolly hair
 - Abnormal nails.

Ectodermal changes seen in incontinentia pigmenti.

- Skin features occur in four stages:

Stage 1 (vesicular) is characterized by the development of red papules and vesicles on an erythematous base. Lesions are seen predominantly on the extremities but may also occur on the trunk or on the head and neck. The vesicular stage has been reported to occur in 90 to 95 percent of patients. In most patients (>90%), lesions are present at birth or develop within the first two weeks of life. They resolve within several months.

Stage 2 (verrucous) is characterized by thickened, warty-appearing linear and whorled plaques on an erythematous base. In general, lesions develop on the extremities and trunk but may also be seen on the head and neck. Verrucous lesions have been reported to occur in 70 to 80 percent of incontinentia pigmenti patients. In most patients, verrucous lesions develop in the first few weeks to months of life and subsequently resolve over weeks to months.

Stage 3 (hyperpigmented) is characterized by the development of streaks and whorls of brown or slate-gray pigmentation. This occurs in 90 to 98 percent of incontinentia pigmenti patients. Hyperpigmented lesions usually involve the trunk but may also involve the extremities, the skin folds, or the head and neck. Hyperpigmented lesions generally develop within the first few months of life and resolve slowly by adolescence.

Stage 4 (atrophic / hypopigmented) is characterized by hypopigmented, atrophic, and reticulate or linear patches observed on the lower extremities, usually

involving the calves. Atrophic lesions usually develop during adolescence and persist into adulthood. Atrophic lesions have been reported to occur in 30 to 75 percent of incontinentia pigmenti patients.

- Hair changes include scarring alopecia and are seen in 28 to 38 percent of patients. An absence or hypoplasia of the eyebrows and eyelashes has also been reported. Finally, hair are sparse in early childhood; later, it has a lusterless, wiry, and coarse appearance.
- Nail features include nail dystrophy, which ranges from mild pitting or ridging of the nail plate to hyperkeratosis and onycholysis.¹⁴ This is observed in 7 to 40 percent of incontinentia pigmenti patients, and usually multiple fingernails and toenails are affected. Nail dystrophy may improve with age. Subungual and periungual keratotic tumors associated with pain, bony deformities, and lytic lesions involving the underlying phalanges also may be seen, usually in older children and adults. The fingers are most commonly affected.
- Dental abnormalities are seen in 80 percent of patients and can involve both deciduous and permanent teeth. Dental anomalies are permanent and thus serve as a very useful diagnostic finding in older patients. Delayed dentition, partial anodontia, and conical or pegged teeth are the most common dental findings. Poor enamel quality leading to an increased incidence of dental caries has been reported historically, but this association has been questioned.^{15,16}
- Ophthalmologic findings:
 - Ophthalmologic findings occur in 20 to 35 percent of patients, and asymmetric involvement is common. Loss of visual acuity and blindness are significant complications. Blindness has been reported to develop in 7 percent of incontinentia pigmenti patients.¹⁷
 - Ophthalmologic manifestations may become evident within the first few weeks to months of life and may progress rapidly to permanent visual deficits.
 - Retinal vaso-occlusive events with resultant ischemia are believed to be the primary mechanism underlying ocular pathology.
 - Retinal manifestations include retinal detachment, proliferative retinopathy, fibrovascular retrolental membranes, foveal hypoplasia, vitreous hemorrhages, and atrophy of the ciliary body.
 - Nonretinal manifestations include strabismus, optic nerve atrophy, conjunctival pigmentation, microphthalmia, keratitis, cataracts, iris hypoplasia, nystagmus, and uveitis.
- Neurologic abnormalities:
 - Neurologic complications occur in 30 percent of incontinentia pigmenti patients and often manifest within the neonatal period.¹⁸

- Seizures are the most common neurologic complication and usually develop within the first few weeks of life.
- Neurologic complications may result in part from microvascular vaso-occlusive ischemic events involving the CNS. Involvement of the cerebral hemispheres, cerebellum, and corpus callosum may occur. Progressive periventricular hemorrhagic infarcts have been reported.
- Other neurodevelopmental manifestations include developmental delay, mental retardation, ataxia, spastic paralysis, microcephaly, cerebral atrophy, porencephaly, hypoplasia of the corpus callosum, and periventricular cerebral edema.
- Other anomalies that have been reported to occur with increased frequency in patients with IP include supernumerary nipples, nipple hypoplasia, and breast hypoplasia.

HISTOPATHOLOGIC FEATURES (FIGS 12.8 AND 12.9)

- Lesional area in incontinentia pigmenti shows spongiosis that manifest as epidermal intercellular edema with exocytosis of numerous eosinophils and mononuclear cells both within the epidermis as well as in spongiotic foci.
- Dyskeratotic keratinocytes are presented adjacent to spongiotic microvesicles. An interstitial infiltrate of lymphocytes and eosinophils is present in the papillary dermis.

Management

1. Treatment is not usually required for the cutaneous lesions. The vesicles of the inflammatory stage should be left intact, and the skin should be monitored for the development of secondary bacterial infections. Emollients and topical antibiotics may be used as needed.
2. Oral hygiene and regular dental care is necessary, and dental restoration may be indicated. Seizures should be treated with anticonvulsants.
3. Routine neurodevelopmental assessments should be made, with referral to occupational and physical therapists as warranted.
4. Frequent ophthalmologic evaluations are required, especially during the first year of life, in order to diagnose and treat potential ophthalmologic complications.
5. Abnormal retinal fibrovascular proliferation can be treated with xenon laser photocoagulation or cryosurgery.¹⁹
6. Retinal detachments may be treated using vitreoretinal surgery.

PACHYONYCHIA CONGENITA

Pachyonychia congenita (PC) is a rare form of hereditary palmoplantar keratoderma (PPK). **Müller** made the first documented observation in 1904.²⁰ It may occur as autosomal

dominant or recessive but sporadic cases do occur. Munro was the first to propose that the genetic defect in PC is linked to the keratin gene cluster on chromosome 17.²¹

ETIOLOGY

It is now clear that pachyonychia congenita results from mutations in the genes encoding epidermal keratinocyte keratins, specifically the 1A and 1B helical encasing regions of keratins K6a, K6b, K16, and K17. The cause for sporadic pachyonychia congenita remains unknown. Currently two distinct syndromes of pachyonychia congenita are recognized: (1) PC-1, or the **Jadassohn-Lewandowsky type**, and (2) PC-2, or the **Jackson-Lawler type**.²² Jadassohn-Lewandowsky type, or PC-1, is the more common variant. Mutations of the genes encoding keratins K6a and K16, which disrupt the keratin filament assembly, characterize the disorder. In PC-2, mutations in the keratin genes K6b and K17 are found.

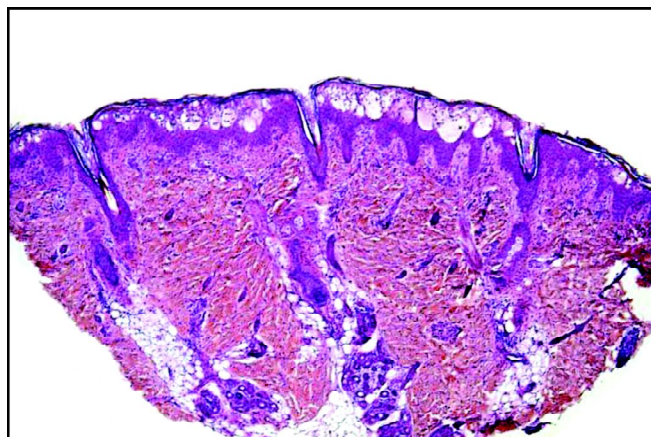


FIGURE 12.8: Histopathologic picture of incontinentia pigmenti showing marked edema of the upper epidermis

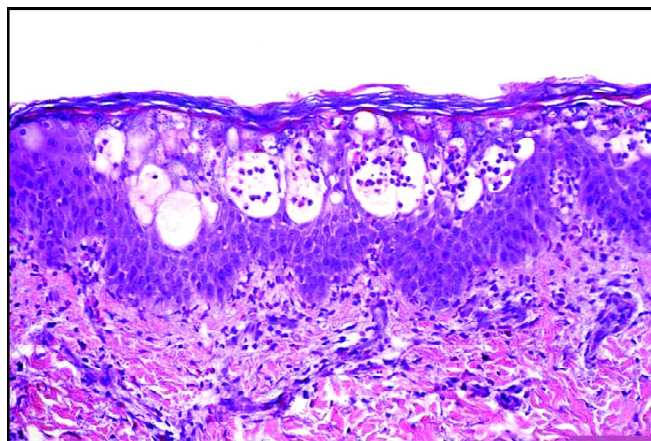


FIGURE 12.9: Histopathologic picture of incontinentia pigmenti showing epidermal spongiosis and an eosinophil-rich cellular infiltrate

CLINICAL FEATURES

- The affected nails are usually present at birth, but they may appear later, as they do in pachyonychia congenita tarda.
- **Paller et al** described five patients in whom the disfigured nails appeared when they were aged 10 to 30 years, as they do in pachyonychia congenita tarda.²³
- Pachyonychia congenita occurs equally in males and females.
- The nail changes are the most prominent feature. The nail plate is substantially thickened and brownish-gray with a rough surface. This is thought to be due to deposition of keratinaceous material in the nailbeds (Fig. 12.10).
- Circumscribed or diffuse hyperkeratoses are expressed on the palms and soles.
- Follicular hyperkeratosis is observed on the face (e.g. temples, front, eyebrows) and on the extensor aspect of the proximal parts of the extremities.
- Leucokeratosis of the oral mucosa is a prominent sign especially of PC-1. Patchy whitish areas may be seen on the back of the tongue, on the buccal mucosa, and, sometimes, on the gingiva. In some patients, early tooth decay is observed.
- PC-2 is characterized by natal teeth and the consistent presence of steatocystoma multiplex.
- A new pachyonychia congenita subtype was described in two patients which included severe and generalized hypotrichia with thickened nails.²⁴
- Sebaceous cysts may appear later in life in case of PC-2.

HISTOPATHOLOGIC FEATURES (FIG. 12.11)

- Lesional areas show marked hyperkeratosis, mostly parakeratosis, acanthosis and perinuclear clearing of epithelial cells.
- Premalignant changes are not observed.

Management

1. The thickened nail plate can be softened by using 20 percent salicylic acid ointment or 20 to 40 percent urea and 10 percent salicylic acid in an emulsifying ointment with occlusive dressings.
2. After the nail plate is softened, it can be mechanically abraded, which is sometimes performed by patients even without softening. This abrasion may be followed by additional softening of the nail plate.
3. A five percent 5-fluorouracil cream can be applied twice daily. 5-fluorouracil cream can be applied after thinning or abrasion of the nail plate to suppress the hyperproliferative activity of the nail matrix.
4. Systemic treatment with retinoids (acitretin, retinoic acid) in a daily dose of 1 mg/kg is partially effective;



FIGURE 12.10: Pachyonychia congenita showing thickened and atrophied nailbeds

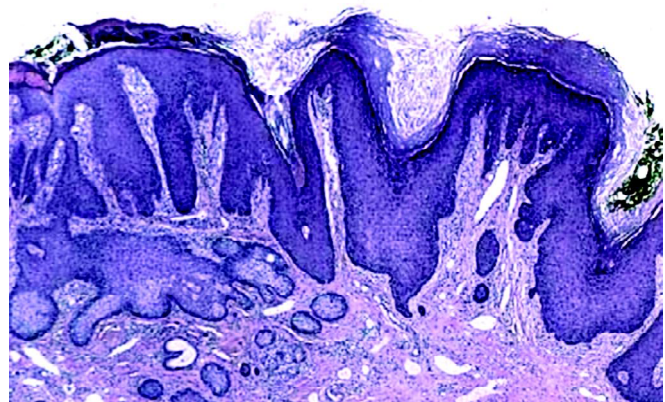


FIGURE 12.11: Histopathologic picture of pachyonychia congenita showing hyperkeratotic epithelium

the nail plate becomes thinner and its surface becomes smoother.

5. Surgical ablation is not recommended, but it can be performed upon a patient's insistence.

EHLERS-DANLOS SYNDROME (FIGS 12.12A AND B)

The Ehlers-Danlos family of disorders is a group of related conditions that share a common decrease in the tensile strength and integrity of the skin, joints, and other connective tissues. The first detailed clinical description of the syndrome is attributed to **Tschernogobow in 1892**.²⁵ The syndrome derives its name from reports by Edward Ehlers, a Danish dermatologist, in 1901 and by Henri-Alexandre Danlos, a French physician with expertise in chemistry of skin disorders, in 1908. It is thought to be caused by various abnormalities in the synthesis and metabolism of collagen (a component of the matrix) and other connective tissue proteins.

MOLECULAR BASIS OF THE DISEASE

See Table 12.1.

CLASSIFICATION

Types of Ehlers–Danlos Syndrome arranged in accordance to its new and previous nomenclatures have been elaborated in Table 12.2.

CLINICAL FEATURES

- It is thought to occur with a frequency of 1 per 5000 to 1 per 10,000.
- Ehlers-Danlos syndromes are heritable disorders. As such, the disorders are present at birth.
- Most of the patients with this syndrome show malformed teeth, large pulp stones and hypoplastic enamel.

Management

1. Any type of medical treatment is unsatisfactory.
2. Extreme caution is mandatory in any surgical maneuver.
3. Plastic re-excision of scars sometimes provides acceptable cosmetic results.

OSLER-WEBER-RENDU SYNDROME (FIGS 12.13A AND B)

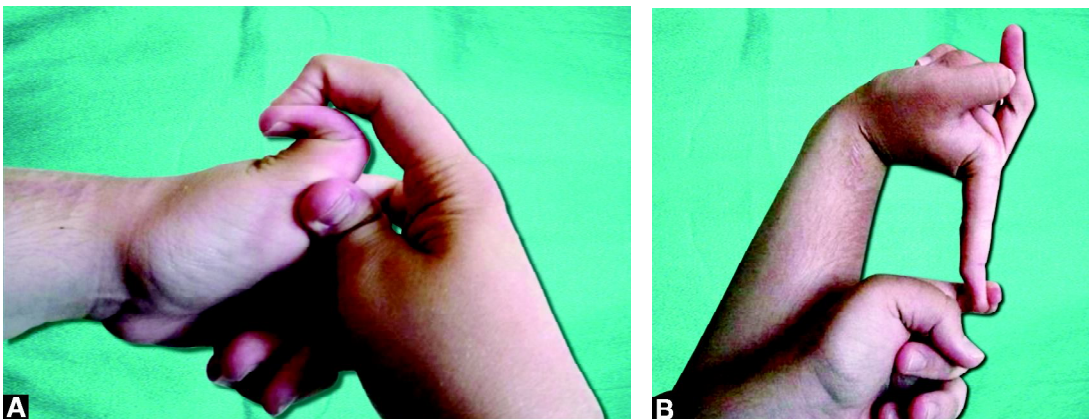
Osler-Weber-Rendu syndrome, also known as hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant disorder typically identified by the triad of telangiectasia, recurrent epistaxis, and a positive family history for the disorder.

ETIOLOGY

- The disease is caused by genetic defects with an autosomal dominant inheritance. So far, two primary loci have been identified associated with Osler-Weber-Rendu syndrome: one on chromosome arm 9q33-34 (HHT1) and a second on chromosome arm 12q11-14 (HHT2).
- Two more genes have recently been implicated; MADH4 gene mutation in patients with a combined syndrome of Osler-Weber-Rendu syndrome and juvenile polyposis and an unidentified HHT3 gene linked to chromosome 5.²⁷

CLINICAL FEATURES

- The worldwide prevalence is 1 case per 5,000 to 10,000 population.



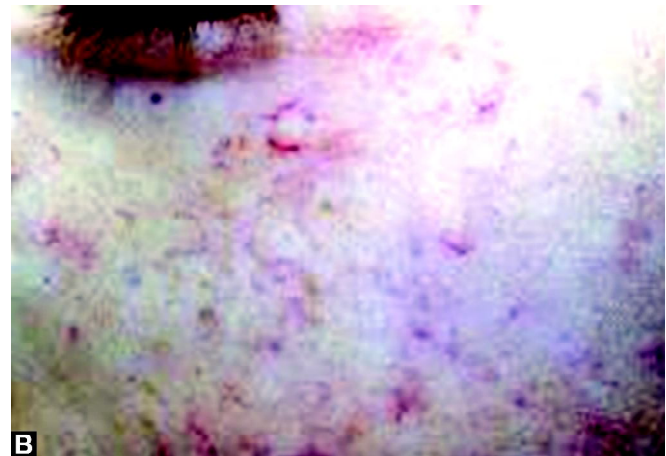
FIGURES 12.12A and B: Ehlers-Danlos syndrome showing hypermobility of the joints

TABLE 12.1: Molecular basis of Ehlers-Danlos syndrome

Type	Old nomenclature	Protein abnormality	Gene abnormality	Chromosome locus
Classic	Type I/II	Type V collagen	COL5A1, COL5A2	9q34.2-34.3 2q31
Hypermobility	Type III	Unknown	Unknown	Unknown
Vascular	Type IV	Type III collagen	COL3A1	2q31
Kyphoscoliosis	Type VI	Lysyl hydroxylase deficiency (some)	PLOD1	1p36.3-36.2
Arthrochalasia	Type VII A/B	Type I collagen	COL1A1 COL1A2	17q31-22.5 7q22.1
Dermatosparaxis	Type VIIC	N-proteinase	ADAMT2	5q23-24

TABLE 12.2: Types of Ehlers-Danlos syndromes²⁶

Type	Inheritance	Previous nomenclature	Major diagnostic criteria	Minor diagnostic criteria
Classic	Autosomal dominant	Types I and II	Skin hyperextensibility, wide atrophic scars, joint hypermobility	Smooth, velvety skin; easy bruising; molluscoid pseudotumors; subcutaneous spheroids; joint hypermobility; muscle hypotonia; postoperative complication (e.g. hernia); positive family history; manifestations of tissue fragility (e.g. hernia, prolapse)
Hypermobility	Autosomal dominant	Type III	Skin involvement (soft, smooth and velvety), joint hypermobility	Recurrent joint dislocation; chronic joint pain, limb pain, or both; positive family history
Vascular	Autosomal dominant	Type IV	Thin, translucent skin; arterial/intestinal fragility or rupture; extensive bruising; characteristic facial appearance	Acrogeria, hypermobile small joints; tendon/muscle rupture; clubfoot; early onset varicose veins; arteriovenous, carotid-cavernous sinus fistula; pneumothorax; gingival recession; positive family history; sudden death of close relative
Kyphoscoliosis	Autosomal recessive	Type VI – lysyl hydroxylase deficiency	Joint laxity, severe hypotonia at birth, scoliosis, progressive scleral fragility or rupture of globe	Tissue fragility, easy bruising, arterial rupture, marfanoid, microcornea, osteopenia, positive family history (affected sibling)
Arthrochalasia	Autosomal dominant	Type VII A, B	Congenital bilateral dislocated hips, severe joint hypermobility, recurrent subluxations	Skin hyperextensibility, tissue fragility with atrophic scars, muscle hypotonia, easy bruising, kyphoscoliosis, mild osteopenia
Dermatosparaxis	Autosomal recessive	Type VII C	Severe skin fragility; saggy, redundant skin	Soft, doughy skin; easy bruising; premature rupture of membranes; hernias (umbilical and inguinal)



FIGURES 12.13A and B: Osler-Weber-Rendu syndrome showing red, nodular and hemorrhagic areas on lip and cheek

- It occurs with equal frequency and severity in both sexes.
- It may be congenital in nature.
- Epistaxis is the most common manifestation of the disease.
- Recurrent painless gastrointestinal bleeding.
- Dyspnea, hemoptysis may be present.
- Migraine headaches, headache, seizures, stroke and brain abscess.
- Visual disturbances may be noted.
- Patients may be cyanotic because of right-to-left pulmonary shunting or pale because of anemia.

Management

1. Septal dermoplasty can reduce the severity of epistaxis by 75 percent. This procedure is performed by replacing the nasal mucosa with autologous skin grafts. Telangiectasias may also develop on the autologous skin grafts.
2. Pulsed dye laser treatment may also be used to photocoagulate telangiectasias in the nasal mucosa.
3. Endovascular embolization for treatment of severe acute epistaxis is also a treatment modality.²⁸
4. Septectomy combined with septal dermoplasty may also be a viable option for patients with severe transfusion-dependent epistaxis.
5. Embolization, ligation, or surgical excision is indicated for enlarging or symptomatic pulmonary arteriovenous malformations.
6. Life-threatening gastrointestinal bleeds are often effectively treated by segmental bowel resection.
7. Embolization of the hepatic artery in selected patients with liver involvement may be used, as well as liver transplantation.
8. Recent recommendations also advocate the use of antibiotic prophylaxis prior to surgical or dental

procedures in all patients with known pulmonary arteriovenous malformations or positive contrast echocardiography findings (agitated saline solution transthoracic contrast echocardiography [TTCE] grade 1 or higher).

PEUTZ-JEGHERS SYNDROME (FIGS 12.14A AND B)

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. The syndrome was described in 1921 by **Jan Peutz**, a Dutch physician who noted a relationship between the intestinal polyps and the mucocutaneous macules in a Dutch family. **Harold Jeghers** (1904–1990), an American physician is credited with the definitive descriptive reports of the syndrome when he published “Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits” in 1949 with **McKusick and Katz**.²⁹ The eponym Peutz-Jeghers syndrome (PJS) was introduced by the radiologist **Andre J. Bruwer** in 1954. The cause of Peutz-Jeghers syndrome (PJS) appears to be a germline mutation of the STK11/LKB1 (serine/threonine kinase 11) tumor suppressor gene in most cases (66–94%), located on band 19p13.3.

CLINICAL FEATURES

- It shows equal predilection for males and females.
- Although the average age at which Peutz-Jeghers syndrome (PJS) appears is 23 years in men and 26 years in women, pigmented lesions are present in the first years of life and may fade at puberty, except for lesions on the buccal mucosa, making the diagnosis possible in pediatric patients.
- Repeated bouts of abdominal pain in patients younger than 25 years.



FIGURES 12.14A and B: Pigmented melanin spots on lip and gingiva

- Unexplained intestinal bleeding in a young patient.
- Prolapse of tissue from the rectum.
- Menstrual irregularities in females (due to hyperestrogenism from sex cord tumors with annular tubules).
- Gynecomastia in males (possible due to the production of estrogens from Sertoli cell testicular tumors).
- Precocious puberty.
- Mucocutaneous pigmentation and melanin spots are typical of patients with Peutz-Jeghers (PJS) syndrome, and they are present in more than 95 percent of cases. They appear as small, flat, brown or dark blue spots with an appearance of freckles, most commonly in the peribuccal area.
- Cutaneous pigmentation is usually located in the perioral region, crossing the vermilion border, in the perinasal and perioral areas, fingers and the toes, on the dorsal and velar aspects of the hands and the feet.

HISTOPATHOLOGIC FEATURES

- Lesional areas from the tissue in Peutz-Jeghers syndrome shows overgrowths in intestinal glandular epithelium supported by core of smooth muscle.
- Cutaneous lesions show acanthotic epithelium with elongation of rete ridges.

Management

1. Annual physical examination that includes evaluation of the breasts, abdomen, pelvis, and testes along with genetic counseling.
2. Annual complete blood cell (CBC) count.
3. Push enteroscopy and interoperative enteroscopy with polypectomy are used to remove larger polyps and may defer the need for repeated small bowel resections.
4. Laparotomy and resection, as indicated, for small intestinal intussusception, obstruction, or persistent intestinal bleeding may be necessary.
5. Surgical treatment of extraintestinal cancers detected by surveillance and diagnosis is required.

WHITE SPONGE NEVUS

White sponge nevus (WSN) is a rare autosomal dominant disorder that predominantly affects nonkeratinizing stratified epithelia such as the oral mucosa. This disease was first described by *Hyde*,³⁰ but the term “white sponge nevus” was coined in 1935 by *Cannon*.³¹

ETIOLOGY

White sponge nevus is thought to be caused by *CK4* or *CK13* point mutations.

CLINICAL FEATURES

- White sponge nevus almost always presents during childhood.
- There is no gender predilection.
- It is characterized by soft, white, and spongy plaques in the oral mucosa. The surface of the plaque is thick, folded, and may peel away from the underlying tissue (Fig. 12.15).
- The buccal mucosa is the most commonly affected site, followed by lips, alveolar ridges, and the floor of the mouth.

HISTOPATHOLOGIC FEATURES

- The histopathologic features of white sponge nevus include epithelial thickening, hyperparakeratosis, and vacuolization of the keratinocytes in the suprabasal layers (Fig. 12.16).
- The entire spinous layer may show intracellular edema with “basket-weave” and “cell-within-a-cell” appearances.
- There are few mitotic figures and there is never any evidence of dysplasia.
- In cytological smears occasional cells will have condensed eosinophilic cytoplasm immediately surrounding the nucleus.

Management

1. No specific treatment is required for white sponge nevus as it remains essentially unchanged after the first few months of onset, except for the rare example of a plaque which extends onto the lip vermilion and is surgically removed for aesthetic reasons.
2. The occasional mildly symptomatic case may respond to topical applications of tetracycline.



FIGURE 12.15: White sponge nevus showing diffuse white area on lateral border of tongue

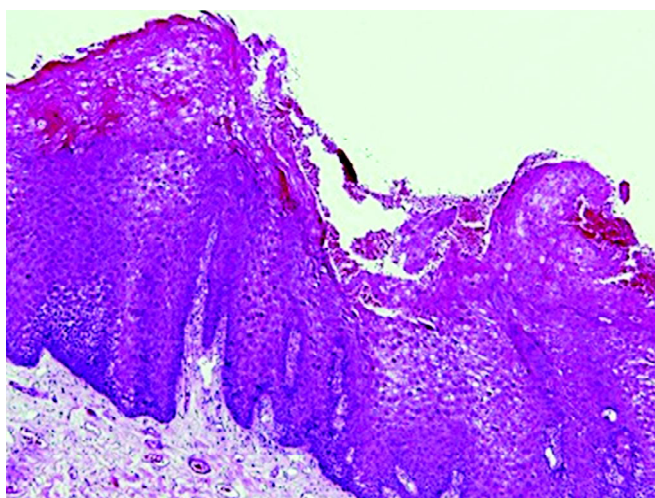


FIGURE 12.16: Histopathologic picture of white sponge nevus showing hyperkeratosis and vacuolization of the keratinocytes in the suprabasal layers

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a rare group of inherited disorders that manifests as blistering or erosion of the skin and, in some cases, the epithelial lining of other organs, in response to little or no apparent trauma.

CLASSIFICATION WITH MOLECULAR BASIS OF EPIDERMOLYSIS BULLOSA³²

See Table 12.3.

CLINICAL FEATURES

Three major categories of epidermolysis bullosa have been identified: The onset of dystrophic epidermolysis bullosa is at birth or early childhood.

1. Epidermolysis bullosa simplex
2. Junctional epidermolysis bullosa
3. Dystrophic epidermolysis bullosa.

Epidermolysis Bullosa Simplex (Fig. 12.17)

- The onset of epidermolysis bullosa simplex is at birth or early infancy.
- The generalized form is inherited as an autosomal dominant trait.



FIGURE 12.17: Epidermolysis bullosa simplex showing multiple vesicles in buttock region

TABLE 12.3: Classification with molecular basis of epidermolysis bullosa

Level of skin cleavage	Major type	Target gene (protein)	Known targeted protein
Intraepidermal (epidermolytic)	Epidermolysis bullosa	<i>PKP1</i> (plakophilin1) <i>DSP</i> (desmoplakin) <i>KRT5</i> (keratin-5) <i>KRT14</i> (keratin-14) <i>PLEC1</i> (plectin) <i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6 \beta 4$ integrin)	Keratins 4 and 14; plectin; $\alpha 6 \beta 4$ integrin; plakophilin-1 desmoplakin
Intra-lamina lucida (lamina lucidolytic)	Junctional epidermolysis bullosa	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332) <i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332) <i>COL17A1</i> (type XVII collagen) <i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6 \beta 4$ integrin) <i>COL17A1</i> (type XVII collagen)	Laminin-332(laminin 5); type XVII collagen; $\alpha 6 \beta 4$ integrin
Sub-lamina densa (dermolytic)	Dystrophic epidermolysis bullosa	<i>COL17A1</i> (type XVII collagen)	Type VII collagen
Mixed	Kindler syndrome	<i>KIND1</i> (kindling-1)	Kindlin-1

- It is characterized by formation of vesicles and bullae on hands and feet. These vesicles rupture and form ulcers. These ulcers heal within one to two weeks without scarring.
- The localized form is also called as familial form that occurs on hands and feet, and also shows recurrence.
- It occurs during childhood or later in life, shows vesicles that get ulcerated and heals without scar formation.

Junctional Epidermolysis Bullosa (Fig. 12.18)

- The onset of junctional epidermolysis bullosa is at birth.
- There is absence of any pigmentation and death occurs within three months of age.
- The lesions occur as vesicles that rupture and form ulcers to such an extent that there occurs shedding of the sheets of skin.
- Similar forms of ulcers are seen in the oral cavity and sometimes there is defect in formation of enamel and dentin.³³

Dystrophic Epidermolysis Bullosa

It occurs in two forms:

1. Dominant and
2. Recessive.

Dominant form

- It occurs in infancy.
- The lesions occur on ankles, elbows, feet and head.
- The vesicles rupture forming ulcers that heal with formation of scar.
- Other clinical features include hyperhidrosis, hypertrichosis and ichthyosis.
- Sometimes bullae occur in the oral cavity.

Recessive form

- It is also known as classic form.
- It is seen at birth and characterized by presence of bullae at buttocks, feet, scapulae, elbows and fingers.



FIGURE 12.18: Junctional epidermolysis bullosa showing shed sheet of skin in upper limb

- The patients show positive Nikolsky sign, i.e. separation of the epithelium with tangential pressure on the skin surface.
- Oral manifestations occur in the form of bullae which is preceded by white spots and localized areas of inflammation.
- Apart from these, rudimentary teeth, congenitally absent teeth and hypoplastic teeth are seen.

HISTOPATHOLOGIC FEATURES (FIG. 12.19)

- Lesional area in simplex form shows intraepithelial clefting.
- Junctional and dystrophic forms show subepithelial clefting.
- Ultramicroscopically, clefting of basement membrane in junctional form occurs at the level of lamina lucida whereas in dystrophic form it occurs below lamina densa.

Management

1. The treatment of epidermolysis bullosa (EB) is primarily preventive and supportive. Once blistering has occurred, the blister should be punctured with a sterile needle or a blade. This may prevent the accumulation of fluid and pressure and may thus prevent the blister from extending.
2. Open wounds should be covered with nonadherent dressings such as petrolatum-impregnated gauze, hydrogels, fenestrated silicone dressings or absorbent foam silicone dressings. Tape and any significant pressure to the skin must be avoided. Dressings can be held in place with rolled gauze (such as Kerlix), with tape applied only to the dressing itself or by stockinette (such as Surgifix or Spandage).³⁴

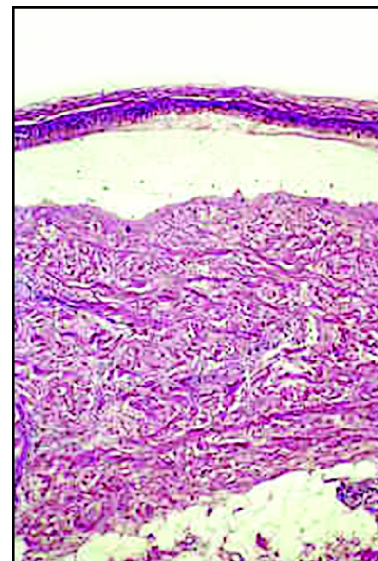


FIGURE 12.19: Histopathologic picture of epidermolysis bullosa showing subepithelial clefting

3. Some authors recommend daily application of polymyxin, bacitracin, or silver sulfadiazine topical ointments to treat open or partially healed wounds, which should be covered with petrolatum-impregnated gauze or nonadherent synthetic dressing. Gentamicin soaks (480 mg/L saline), acetic acid soaks (white vinegar), and the addition of small amounts of bleach to the bath water (e.g.: 1/8 cup per full tub) have been used to decrease the overgrowth of pseudomonas and staphylococcal organisms.
4. Surgical procedures can correct the deformities of epidermolysis bullosa caused by repeated episodes of blistering and scarring of the hand. Esophageal dilatation or insertion of a gastrostomy tube may be required if esophageal strictures develop.
5. Patients with limited donor sites for a skin graft may need advanced therapy with bioengineered skin products. Several products (e.g.: composite cultured skin [CCS], Graftskin, Dermagraft) have been used in the treatment of patients with epidermolysis bullosa.

PEMPHIGUS

Pemphigus is a group of autoimmune diseases of the skin and/or mucous membranes that cause burn-like lesions or blisters that do not heal. The term was originally named by **Wichman** in 1791.³⁵

CLASSIFICATION

There are basically three types of pemphigus:

- Pemphigus vulgaris (PV) (Fig. 12.20)
- Pemphigus vegetans
- Pemphigus foliaceus (PF).

CLINICAL FEATURES

- The clinical features of pemphigus are essentially similar in children to that of adults.
- In children, most commonly seen pemphigus is fogo selvagem which is a subtype of pemphigus foliaceus, followed by pemphigus vulgaris.
- Mean age of onset is 12 years.³⁶
- Boys have a lower mean age of onset as compared to girls.
- Occurrence is most common in males with a male to female ratio of 1:0.96.
- Certain aggravating factors have been associated with childhood pemphigus vulgaris similar to adults. This includes drugs like enalapril³⁷ and monteleukast³⁸ and vaccination with diphtheria-tetanus toxin.³⁹
- Lesions appear as flaccid vesicles on erythematous or normal skin which break easily to form erosions and crust.



FIGURE 12.20: Pemphigus vulgaris showing multiple vesicles on forearm

- Nikolsky sign, i.e. separation of the epithelium with tangential pressure on the skin surface is positive.
- Involvement of mucous membrane, mainly the oral mucosa, has been seen in almost all cases and usually precedes the cutaneous lesions.
- Oral lesions are seen in the form of superficial, ragged erosions and ulcerations distributed along the palate, labial mucosa, ventral surface of the tongue and gingiva.
- Ocular involvement occurs in the form of bilateral conjunctivitis.

HISTOPATHOLOGIC FEATURES

- The blistering or cleavage in this disease occurs above the basal layer of the epithelium, typically leaving a layer of basal cells with rounded tops, reminiscent of “**tombstones**”.
- The intact bulla is filled with serum and occasional sloughed, rounded, keratinocytes resembling “**fried eggs**”, with large, hyperchromatic nuclei and a rim of eosinophilic cytoplasm. The latter acantholytic cells, called **Tzanck cells**, are best seen in the smear sample of a fresh blister (**Tzanck test**). The suprabasal bulla frequently contains chronic and acute inflammatory cells, including eosinophils (Fig. 12.21).
- Direct immunofluorescence of perilesional mucosa shows a lacy or chicken-wire pattern of deposits around individual spinous cells of the epithelium (Fig. 12.22).
- IgG is almost always the deposited immunoglobulin, but IgM and IgA are seen in almost half of all cases.

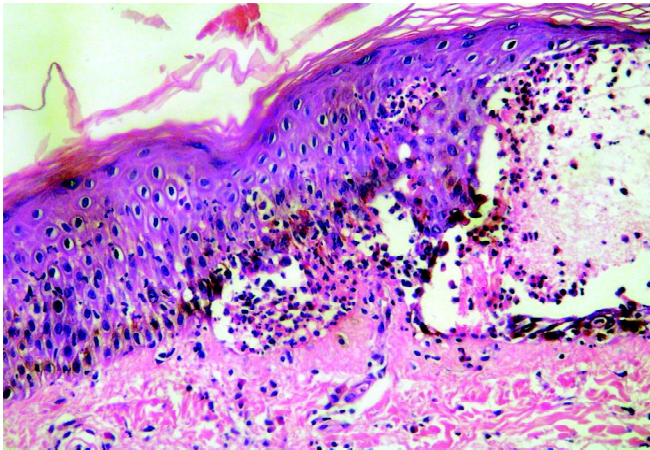


FIGURE 12.21: Histopathologic picture of pemphigus vulgaris showing suprabasilar bulla containing inflammatory cell infiltrate

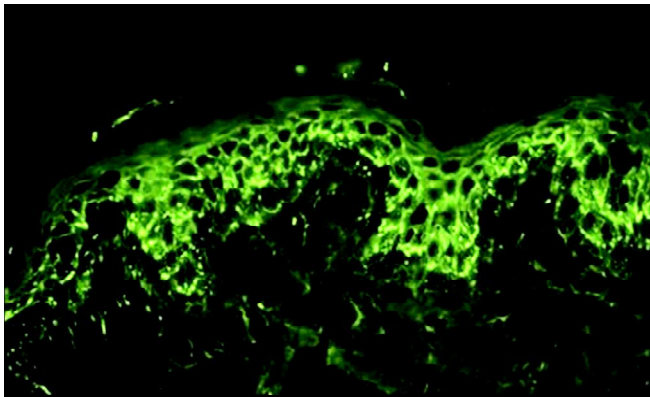


FIGURE 12.22: Direct immunofluorescence showing intercellular immunoglobulin G throughout the epidermis of a patient with pemphigus vulgaris

Management

1. Oral corticosteroids have been used with some success but, Cushing's syndrome, growth retardation and infection are the most common side effects seen in children.
2. Bjarnason et al have suggested an initial dose in the range of 2 to 3 mg/kg/day with slow tapering to 5-8 mg/kg/day in approximately two weeks following alternate day schedule for further reduction.⁴⁰
3. Methylprednisolone pulse (1 gm/day IV for 5 days) and dexamethasone pulse (136 mg of dexamethasone/day IV for 3 consecutive days) has also been used successfully in severe cases with high antibody burden.

4. Topical and intralesional steroids have been used for single recalcitrant lesion to avoid escalation of systemic dose.
5. When a high dose prednisolone is required to control the disease, multiple adjuvants such as azathioprine have been used in children. Bjarnason et al suggested 2 mg/kg/day to be used initially in two divided doses followed by maintenance dose of 1 mg/kg/day.
6. Paltzik et al successfully used gold in intramuscular form as aurothioglucose or aurothiomalate or in oral form as auronofin in children in dose of 15 mg/week for 32 weeks.
7. Methotrexate was used by Faure et al in a dose of 20 mg IM/week.⁴¹
8. Other adjuvants that have been used are dapsone 100 to 200 mg per day, cyclophosphamide in dose of 50 mg/day and plasmapheresis. Recently a 17-year-old female with 10 year history of pemphigus vulgaris refractory to azathiopurine, mycophenolate mofetil (2 gm/day), prednisolone (2 mg/kg/day), IVIg (1gm/kg) and plasmapheresis was treated successfully with anti CD 20 antibody Rituximab (375 mg/m²sub) with decline in circulating anti Dsg 1 and Dsg 3.⁴²

PEMPHIGUS FOLIACEOUS

Pemphigus foliaceus (PF) is generally a benign variety of pemphigus. It is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis), resulting in the formation of superficial blisters. **Pierre Louis Alphe Cazenave** documented the first description of pemphigus foliaceus in 1844.

CLASSIFICATION

Pemphigus foliaceus has the following six subtypes:

1. Pemphigus erythematosus (PE)
2. Pemphigus herpetiformis (PH)
3. Endemic pemphigus foliaceus
4. Endemic pemphigus foliaceus with antigenic reactivity characteristic of paraneoplastic pemphigus (but with no neoplasm)
5. Immunoglobulin A (IgA) pemphigus foliaceus, and
6. Drug-induced pemphigus foliaceus.

Endemic pemphigus foliaceus or fogo selvagem occurs most commonly in children and thus has been described here in detail. The role of genetic factors is evident in fogo selvagem in which a strong association exists with some human leukocyte antigen DRB1 (HLA-DRB1) haplotypes, including DRB1*0404, 1402, 1406, and 1401.

CLINICAL FEATURES

- Endemic pemphigus foliaceus, or fogo selvagem, occurs with a high frequency in central and southwestern Brazil and in Colombia. The Terena reservation in Brazil, a recently identified focus, has a prevalence of 3.4 percent of the population.⁴³
- Fogo selvagem often occurs in children, young adults, and genetically related family members. Metry et al 2002, in a review of 28 cases reported that the average age at presentation of this lesion was 7.7 years.⁴⁴
- Childhood pemphigus foliaceus is slightly more common in boys with M:F ratio of 1.33:1.
- Triggering factors for occurrence of this lesion are sunlight, drugs, bacterial infection, cytomegalovirus infection and otitis.
- Majority of children are asymptomatic.
- Metry et al, 2002 reported the presence of crusted plaques, and erosions were the most common primary lesions in their review of 28 cases.
- Lesions appear vesiculobullous, which later on rupture to produce painful ulcers.
- An unusual circinate/arcuate/polycyclic pattern which is a specific presentation in children has been described in a few patients.⁴⁵
- When direct immunofluorescence is performed, the antibody titer does not appear to correlate with the severity and extent of skin disease.

HISTOPATHOLOGIC FEATURES

- Lesional areas in pemphigus foliaceus show acanthosis in upper layers of epithelium.
- Separation of epithelium occurs without bulla formation.
- Epithelium may show hyperkeratosis or parakeratosis and dyskeratotic cells within the granular cell layer.
- Dermal lymphocytic infiltration with presence of eosinophils is also evident.

Management

1. Use of topical steroid is often recommended.
2. Dapsone is the most commonly used adjuvant.
3. Other therapies include erythromycin, chloroquine, methotrexate, sulfapyridine, azathioprine and hydroxychloroquine.

PEMPHIGUS VEGETANS

Pemphigus vegetans is a localized form of pemphigus vulgaris.

CLASSIFICATION

This rare form of pemphigus vulgaris has two variants:

- Neumann and
- Hallopeau.

In both types, oral lesions are common. This is a rare lesion and only three cases of pemphigus vegetans have been reported till 2004 in children.

Neumann type: In this type, antibody is directed against 130 and 85 kDa (kilo Dalton) polypeptides of the pemphigus vulgaris antigen.

- **Clinical features:** Initially, the lesions appear vesicular erosive resembling pemphigus vulgaris evolving into vegetating plaques.
- **Histopathologic features:** In the Neumann type, there are intraepidermal vesicles with suprabasilar acantholysis. No eosinophilic microabscesses are present.

Hallopeau type: In this type, antibody is directed against 130 kDa (kilo Dalton) polypeptide.

- **Clinical features:** Initially, the lesions appear pustular with a benign course and few relapses.
- **Histopathologic features:** In the Hallopeau type, eosinophilic spongiosis and microabscesses are present. In the later vegetative plaques, there is prominent epidermal hyperplasia with hyperkeratosis, papillomatosis, and occasional acantholysis.

Management

Higher doses of steroids are usually prescribed.

PEMPHIGUS ERYTHEMATOSUS

Pemphigus erythematosus (PE), also known as **Senear-Usher syndrome**, is an overlap syndrome with features of lupus erythematosus (LE) and pemphigus foliaceus.

ETIOLOGY

Certain HLA haplotypes (A10 or A26, DRW6) are thought to be associated, suggesting a genetic predisposition. In pemphigus erythematosus, the target antigen for the antibodies is desmoglein 1.

CLINICAL FEATURES

- Kumar KA, 2008, reported a high prevalence of 4.4 cases per million population, with a high preponderance (61.5%) in females.⁴⁶
- Pemphigus erythematosus is considered a variant of pemphigus foliaceus rather than a distinct entity.
- Pemphigus erythematosus may occur at any age, but it is unusual in children. Four cases of pemphigus erythematosus in children have been reported till date.
- Lesions typically involve the scalp, face, upper part of the chest, and back.
- Patients with pemphigus erythematosus classically present with small, flaccid bullae with scaling and crusting. Occasionally, the appearance may suggest a papulo-squamous disorder.

- Secondary infection may occur, resulting in impetiginization, healing with pigment changes, and scarring.
- On the face, pemphigus erythematosus presents on the bridge of the nose and on the malar areas as in the butterfly distribution seen in lupus erythematosus.

HISTOPATHOLOGIC FEATURES

The histology is identical to pemphigus foliaceus with a subcorneal blister and acantholysis.

Management

1. Topical corticosteroids are useful for patients with limited disease or as an adjunct to systemic therapy.
2. Systemic steroids have been the mainstay of therapy for widespread pemphigus since their first use in 1950. Prednisone 1 to 2 mg/kg/d as a single morning dose or as intravenous pulses may control the disease.
3. Dapsone is effective in some patients with pemphigus erythematosus. But pediatric dose had not been established yet.
4. Azathioprine is a potent immunosuppressive agent that has been used as a steroid-sparing agent. Initial dose of 2 to 5 mg/kg/d PO/IV and maintenance dose of 1 to 2 mg/kg/d PO/IV has been administered.

PARANEOPLASTIC PEMPHIGUS (FIG. 12.23)

Anhalt et al 1990, first described paraneoplastic pemphigus in five patients with underlying neoplasms who developed oral erosions and bullous skin eruptions.⁴⁷ By immunoprecipitation, target antigens were identified from skin extracts with molecular weights of 250, 230, 210, and 190 kDa.



FIGURE 12.23: Paraneoplastic pemphigus showing oral erosions

CLINICAL FEATURES

- Paraneoplastic pemphigus affects children and adolescents aged 8 to 18 years.
- Lesions are seen in both sexes equally.
- The earliest and most constant clinical finding in paraneoplastic pemphigus is painful oral erosions. The erosions can occur anywhere in the mouth, including the buccal, labial, gingival, and lingual mucosae. All surfaces of the oropharynx can be affected.
- Epistaxis is seen due to nasal ulcers.
- Patients may present with diffuse erythema, vesiculobullous lesions, papules, scaly plaques, exfoliative erythroderma, erosions, or ulcerations. The erythema can be macular, urticarial, or targetoid, and it may be polymorphous. Patients may initially present with erythema, and they may subsequently develop bullae and erosions.
- Large areas of denudation with a positive Nikolsky sign can occur.

HISTOPATHOLOGIC FEATURES

Mimouni et al 2002, reported four patterns of involvement of the lesional tissue histopathologically:⁴⁸

1. Sulli
2. Lichenoid infiltrate with cell necrosis
3. Intraepithelial acantholysis
4. Combination of the above.

Pattern 3 was found to be most common.

Management

1. Warm compresses, nonadherent wound dressings, and topical antibiotic ointment are helpful.
2. Potent immunosuppressive agents are required to decrease blistering, but they are often ineffective. High-dose corticosteroids are first-line therapy, followed by steroid-sparing agents such as azathioprine, cyclosporine, and mycophenolate mofetil.⁴⁹
3. Other therapeutic options include plasmapheresis, immunophoresis, intravenous gammaglobulin, and stem cell ablation therapy with high-dose cyclophosphamide without stem cell rescue.
4. Rituximab has been tried in several patients with mixed results.
5. For solid neoplasms, curative resection should be attempted when appropriate.

IMMUNOGLOBULIN A PEMPHIGUS

Immunoglobulin A (IgA) pemphigus is a group of newly characterized immune-mediated intraepidermal blistering skin diseases.

ETIOLOGY

Unlike typical immunoglobulin G (IgG)–mediated pemphigus, IgA pemphigus is characterized by tissue-bound and circulating IgA autoantibodies that target the desmosomal proteins of the epidermis. At least three desmosomal components, including desmoglein 3 (in intraepidermal neutrophilic–type [IEN-type] IgA pemphigus), desmoglein 1, and desmocollin 1 (in subcorneal pustular dermatosis–type [SPD-type] IgA pemphigus foliaceus), have been identified as target antigens in IgA pemphigus.

CLINICAL FEATURES

- It is rarely seen in children and eight cases have been reported in children till date including a 1 month old infant.
- A review of 28 cases reported from 1982-1997 revealed a male-to-female ratio of 1:1.33.
- Lesions form within erythematous plaques but also can form in skin without plaques. The initial, clear, fluid-filled blisters fill with neutrophils and transform into pustules.
- The trunk and proximal extremities, scalp and postauricular areas, and intertriginous areas (axillary and inframammary areas) are involved.
- Mucous membranes, palms, and soles usually are spared.

HISTOPATHOLOGIC FEATURES

Histopathologically, epidermal acantholysis and neutrophil infiltration predominate, hence the synonyms intraepidermal neutrophilic IgA dermatosis, intraepidermal IgA pustulosis, IgA herpetiform pemphigus, and intercellular IgA vesiculopustular dermatosis have been used to describe this group of diseases.

Management

1. Generally, corticosteroids are the mainstay of treatment.
2. Dapsone also may be helpful because of its antineutrophilic effects.
3. Rapid response to treatment with adalimumab and mycophenolate mofetil was reported in 2005.⁵⁰

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Infectious Diseases in Children

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CHAPTER OVERVIEW

Introduction

Bacterial infections of the oral cavity:

Scarlet fever
Diphtheria
Tuberculosis
Leprosy
Syphilis
Actinomycosis
Noma
Tetanus

Mycotic infections of the oral cavity:

Candida albicans

Viral infections of the oral cavity:

Herpes simplex virus
Smallpox
Measles (Rubeola)
Rubella
Herpangina
Cytomegalovirus infection
AIDS

INTRODUCTION

The oral flora is one of the most diverse microbial populations known to man. It contains at least 350 different cultivable species. The oral cavity provides some unique habitats for bacterial colonization including teeth, mucosal surfaces, gingival crevices, etc. Normally the oral flora exists in harmonious relationship with the host. This relationship can be altered if normal oral environment is changed. The term infection is used to refer specifically to infectious diseases, which are clinically evident diseases that result from the presence of pathogenic microbial agents, including viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions. Disease word itself implies any deviation from or interruption of the normal structures or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology and prognosis may be known or unknown. This chapter focuses on various diseases pertaining to children.

BACTERIAL INFECTIONS OF THE ORAL CAVITY

SCARLET FEVER (SCARLATINA)

Scarlet fever is an infection produced by group A β -hemolytic streptococci, which are gram-positive microorganisms

occurring in chains (Fig 13.1). Incubation period for this bacterium is three to five days. These bacteria produce a clear, colorless zone of hemolysis within which red cells are completely lysed (Fig. 13.2).

CLINICAL FEATURES

- Occurrence in children is most common
- Clinical manifestations of fever, malaise, chills and vomiting are seen
- Enlargement of regional lymph nodes, especially cervical lymph nodes
- Presence of diffuse, bright red skin rash particularly in areas of skin folds. Such lines appear on 2nd or 3rd day and are known as "**Pastias lines**"
- Rash begins on upper trunk, spreads towards the extremities, sparing the palms and soles
- Desquamation of skin after a few days denotes terminal stages of the disease
- Palate and throat appear fiery red and congested
- Tonsils and faucial pillars are congested, swollen and show the presence of a grayish membrane
- Initially the tongue appears whitish due to presence of a coating on it. Later on due to loss of the coating, the

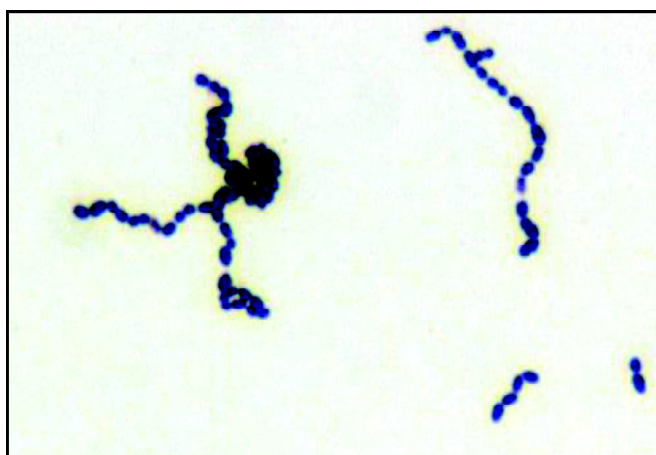


FIGURE 13.1: Streptococci (occurring in chains)



FIGURE 13.3: Raspberry tongue



FIGURE 13.2: Group A -hemolytic streptococci

hyperemic and swollen fungiform papillae appear projecting on the tongue, giving the tongue “**Raspberry**” appearance (Fig. 13.3).

DIAGNOSIS

- Made on the basis of cultures from the throat secretions
- Detection of antigens specific for group A -hemolytic streptococci
- Dick test which is a test to determine susceptibility or immunity to scarlet fever by an injection of scarlet fever toxin.

Management

1. Use of antibiotics.
2. Topical relief of symptoms by application of mupirocins ointment.

COMPLICATIONS

If left untreated, it may lead to peritonsillar abscess, rhinitis, sinusitis, otitis media, meningitis, pneumonia, glomerulonephritis, rheumatic fever and arthritis.

DIPHTHERIA

It is an acute, life-threatening, contagious bacterial infection caused by gram-positive bacillus, *Corynebacterium diphtheriae* showing ‘**wneiform appearance**’ in Gram stain (Fig. 13.4). Humans being the sole reservoirs, the infection mainly spreads via droplet inhalation. Incubation period ranges from two to five days.

CLINICAL FEATURES

- Occurrence in children is most common, especially during winter season
- Clinical manifestations of fever, malaise, chills, headache, anorexia and vomiting are seen
- Enlargement of regional lymph nodes, especially cervical lymph nodes
- A patchy, yellowish-white thin film covered by grayish adherent membrane is seen known as “**diphtheritic membrane**” (Fig. 13.5)
- Raw bleeding surface is seen left when this membrane is stripped off
- Due to involvement of soft palate, uvula, larynx and trachea, there occurs sore throat, stridor and respiratory difficulties
- In severe cases, paralysis of soft palate can be seen.

DIAGNOSIS

- Made on the basis of cultures from the surface of the membrane and also from nasal secretions.

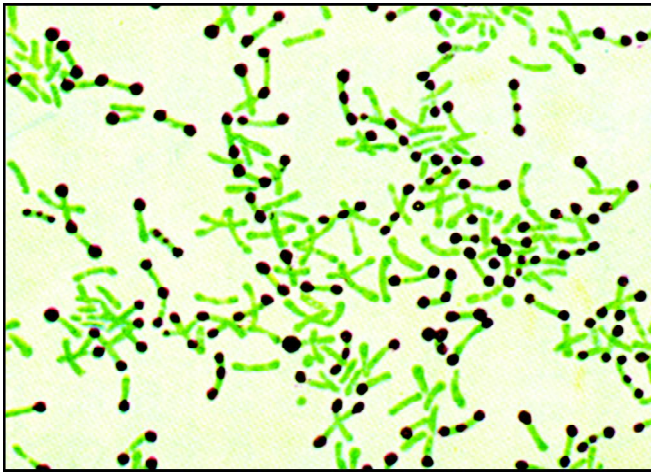


FIGURE 13.4: *Corynebacterium diphtheriae* "cuneiform appearance"

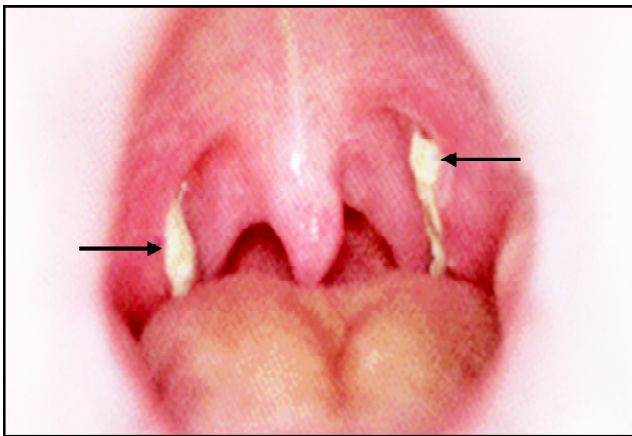


FIGURE 13.5: Grayish adherent "diphtheritic membrane (arrows)"

Management

1. Prophylactic active immunization with diphtheria toxoid.
2. Use of antitoxin in combination with antibiotics.

COMPLICATIONS

If left untreated, may lead to myocarditis, polyneuritis and acute interstitial nephritis.

TUBERCULOSIS

It is a chronic granulomatous disease caused by acid fast bacillus *Mycobacterium tuberculosis* which appears as straight or slightly curved slender rods (Fig. 13.6).

CLASSIFICATION

There are three types of tuberculosis:

1. **Primary tuberculosis:** Occurs in people who were not exposed previously to the infection

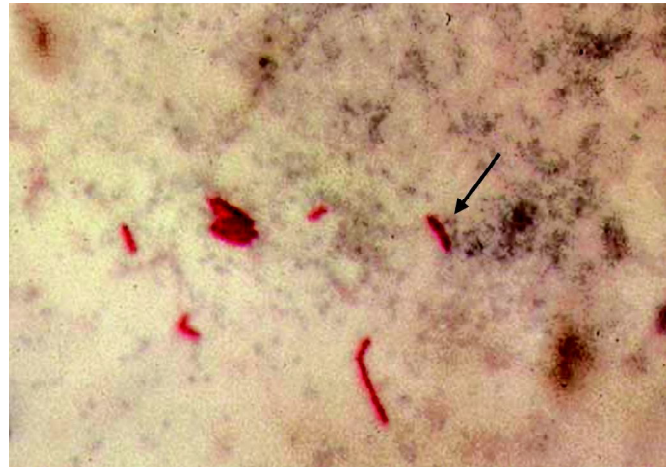


FIGURE 13.6: Tubercle bacilli (arrow)

2. **Secondary tuberculosis:** Occurs in people who have been previously infected in their later life due to activation of the micro-organism
3. **Miliary tuberculosis:** In which there is diffuse dissemination through vascular system.

CLINICAL FEATURES

- Fever, malaise, chills
- Night sweats, loss of weight, easy fatigability
- Persistent cough, lymphadenopathy
- '**Scrofula**' is the term given for infected and enlarged submandibular and cervical lymph nodes (Fig. 13.7)
- Primary tuberculosis of skin appearing as papular eruptions and having a tendency for ulceration is termed as '**Lupus vulgaris**' (Fig. 13.8)
- Involvement of tongue in oral cavity is most common
- Tuberculosis may also involve the bone of the maxilla or mandible
- Although rare, lesion in the oral cavity may occur either due to hematogenous spread (anachoretic effect) or due to exposure to the infected sputum
- The gingival lesion appears as diffuse, hyperemic and nodular
- In case of an open cavity, if the micro-organism enters the periapical region, there is formation of periapical granuloma termed as '**Tuberculoma**'.

HISTOPATHOLOGIC FEATURES (FIG. 13.9)

Lesional tissue reveals presence of granuloma containing central area of caseous necrosis surrounded by epithelioid cells, lymphocytes and giant cells.

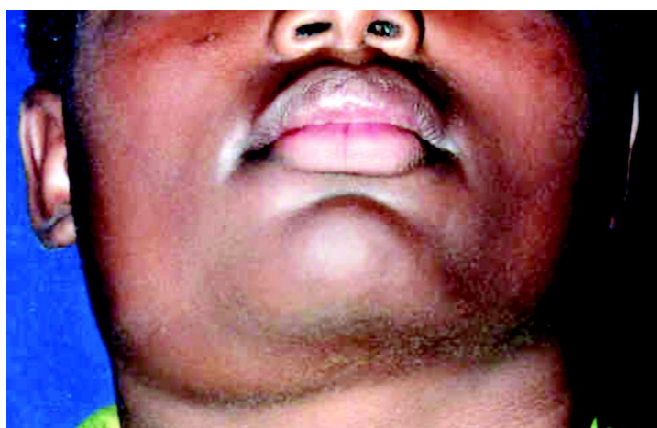


FIGURE 13.7: Scrofula (Tuberculous lymphadenitis)

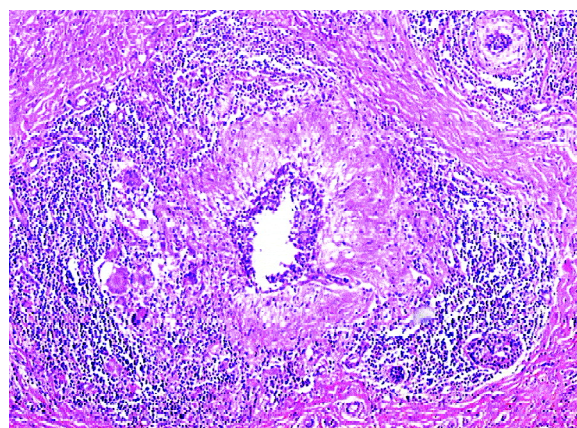


FIGURE 13.9: Histopathologic picture showing caseation seen in tuberculosis



FIGURE 13.8: Lupus vulgaris

DIAGNOSIS

- Mantoux test (tuberculin test)
- Sputum examination for micro-organisms with the help of Ziehl-Neelsen stain.

Management

1. Two multiagent protocols are recommended as first line therapy against drug susceptible tuberculosis:
 - a. Isoniazid + Rifampin for 9 months
 - b. Isoniazid (INH), rifampin and pyrazinamide for 2 months followed by INH and Rifampin for 4 months.
2. Other first line medications include ethambutol and streptomycin. Adverse effects limit the use of these drugs in children.

LEPROSY (HANSEN'S DISEASE)

Leprosy is a chronic granulomatous disease caused by infection with *Mycobacterium leprae*. *M. leprae* was first described in 1873 when **Gerhard Armauer Henrik Hansen** discovered it while examining lymph nodes and other tissues obtained from patients with leprosy. The microorganism appears as a straight or slightly curved rod, similar to tubercle bacilli, but are less acid fast as compared to tubercle bacilli (Fig. 13.10).

PATHOGENESIS

- The exact mechanism of *M. leprae* transmission remains unknown; however, direct human-to-human contact, contact with respiratory secretions from infected individuals, and vertical transmission have been considered the most likely routes of transmission. Most pathophysiological changes observed in leprosy are caused by the ability of *M. leprae* to survive in macrophage cells. Although the incubation period of *M. leprae* can be several decades, it generally averages 5 to 7 years.¹
- Once infected, both cell-mediated and humoral responses are elicited by bacterial antigen DNA glycolipids. Lipoarabinomannan, a component of the cell membrane, induces immune suppression by inhibiting the interferon gamma mediated activation of macrophages.

CLINICAL FEATURES

- The WHO has estimated the global prevalence of leprosy to be 10 to 12 million cases, with most reported in Africa and Asia, particularly in the Indian subcontinent.
- The worldwide incidence rate is 2 cases per 10,000 population. In some areas, as many as 10 percent of cases develop in children younger than 15 years, among whom paucibacillary forms are more frequent.²

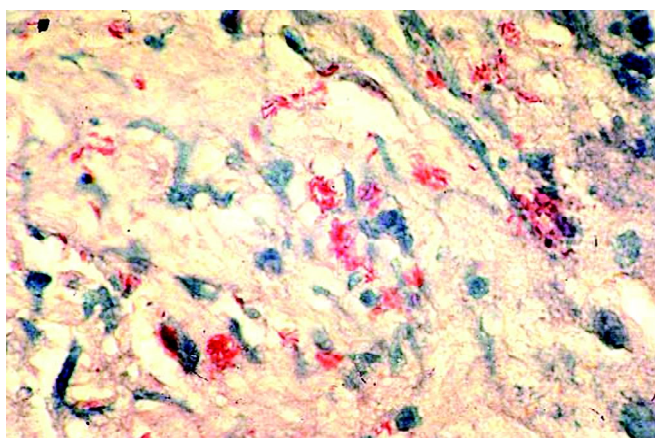


FIGURE 13.10: Lepra bacilli



FIGURE 13.11: Lepromatous leprosy

- Hypoesthesia is the clinical manifestation of peripheral nerve involvement and is present in as many as 70 percent of children with this condition.
- The male-to-female ratio is 2:1 to 3:1.
- Depending on the number of lesions and the number of bacilli observed on the lesion's smear, leprosy can be classified into the following three groups:
 1. **Borderline leprosy:** This is characterized by the presence of single or multiple skin lesions with a raised central area.
 2. **Paucibacillary (tuberculoid) leprosy:**
 - Tuberculoid leprosy presents with one or few (usually < 5) hypopigmented and hypoesthetic lesions. Sensory loss is frequently observed around the lesions.
 - Patients with tuberculoid leprosy have a characteristic normal cell-mediated response to *M. leprae* antigens.
 3. **Multibacillary (lepromatous) leprosy:**
 - Lepromatoid leprosy usually presents with multiple (> 5) poorly defined, hypopigmented or erythematous lesions associated with hypoesthesia. It is also associated with the presence of papules, macules and nodular lesions. Necrotizing erythema nodosum has occasionally been reported in children.
 - Patients with advanced lepromatous leprosy may present with loss of eyelashes or eyebrows and nasal septum perforation. The constellation of disfiguring facial features associated with this disease is named **leonine facies** (Fig. 13.11).
 - The peripheral neuropathy observed in lepromatous leprosy causes muscle weakness and atrophy and has been associated with clawhands and foot drops.
- Other clinical manifestations of lepromatous leprosy include corneal opacifications, keratitis, iritis, testicular atrophy and kidney disease resulting in renal failure.
- Patients with lepromatous leprosy present with characteristically abnormal cell-mediated responses to *M. leprae* antigens.
- **Erythema nodosum leprosum (ENL)** is a condition observed in patients with borderline and lepromatous leprosy. It is usually associated with neuritis, fever and arthralgias. The development of ENL has been suggested to be caused by the presence of immune complexes.
- The development of nonhealing ulcers in the lower extremities of patients with lepromatous leprosy secondary to arthritis is known as the **Lucio phenomenon**. These ulcerations are more common in individuals of Latin American descent and are associated with a high mortality rate.
- Neuropathic pain can be sequelae of multibacillary leprosy that can present more than 10 years after completion of therapy.
- Apart from these generalized signs and symptoms, orofacial lesions observed are:
 - Facial paralysis
 - Lepromas
 - Gingival hyperplasia
 - Loosening of teeth.

HISTOPATHOLOGIC FEATURES (FIG. 13.12)

- Lesion is in the form of a granulomatous nodule.
- It shows a collection of epithelioids, histiocytes, lymphocytes, Langhans type giant cells, vacuolated macrophages (lepra cells).

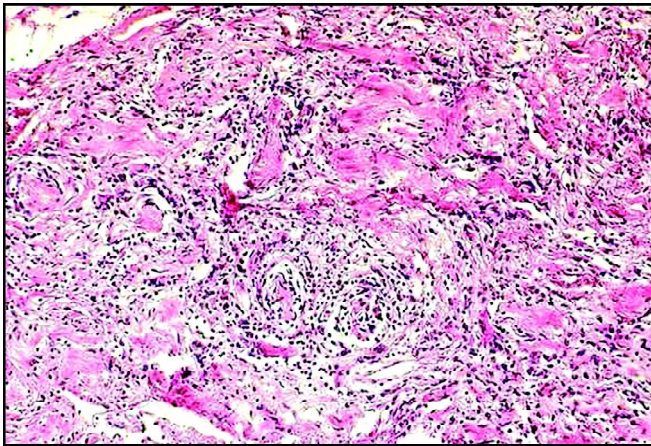


FIGURE 13.12: Histopathologic picture showing granulomatous nodule seen in leprosy

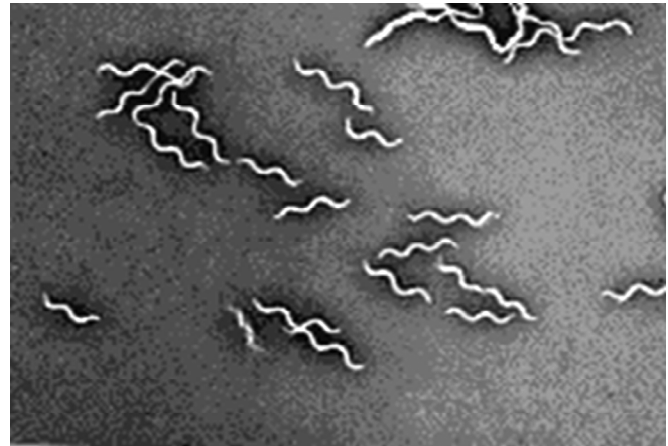


FIGURE 13.13: Spirally arranged *Treponema pallidum*

DIAGNOSIS

- Diagnosis is usually made on the basis of culture of organisms from the lesional area, nasal smears and scrapings, skin biopsy and nerve biopsy, inoculation in foot pad of nine banded armadillo, histamine test, serological tests like Enzyme linked immunosorbent assay (ELISA) and Polymerase chain reaction (PCR).

Management

1. Prolonged therapeutic regimens have traditionally been recommended in the treatment of leprosy; however, recent recommendations by the WHO focus on regimens with shorter duration for both tuberculoid (paucibacillary) and lepromatous (multibacillary) leprosy.
2. The drugs that are more frequently used in the treatment of leprosy include rifampin, dapsone, clofazimine, ofloxacin, minocycline and clarithromycin. Multidrug therapy is required in all cases to prevent antimicrobial resistance.
3. For multibacillary leprosy, the standard regimen should include rifampin, dapsone, and clofazimine. For paucibacillary leprosy, rifampin is usually prescribed in combination with dapsone. For single-lesion paucibacillary leprosy, a single dose of rifampin combined with single doses of ofloxacin and minocycline is recommended.
4. Recent studies suggest that vaccination with Bacille Calmette-Guérin (BCG) during the neonatal period may be protective against leprosy.

SYPHILIS

Syphilis is a sexually transmitted disease (STD) caused by infection with a spirochete named '*Treponema pallidum* (Fig. 13.13) (*T. pallidum*).’ The genus name, *Treponema*, is derived from the Greek term for “turning thread.” Pathogenic

members of this genus include *T. pallidum*, *Treponema pertenue* and *Treponema carateum*. Between 1905 and 1910, **Schaudinn and Hoffman** identified *T. pallidum* as the cause of syphilis.³

CLASSIFICATION

- Acquired syphilis
- Congenital syphilis

ACQUIRED SYPHILIS

The acquired form of syphilis is contracted primarily as a venereal disease, after sexual intercourse with an infected partner, but it may also be acquired by professionals like dental surgeons, nurses or other individuals while carelessly handling the infected patients.

There are three stages in which acquired syphilis occurs:

1. Primary syphilis
2. Secondary syphilis
3. Tertiary syphilis.

PRIMARY SYPHILIS

- It has an incubation period averaging about 21 days.
- The characteristic primary lesion of syphilis is called “**chancere**” and it is a solitary, painless, indurated, non-tender, non-hemorrhagic ulcerated or eroded lesion.
- The oral lesions of primary syphilis occur on the lips, tongue, palate, gingiva, uvula, tonsils, etc. usually three weeks after contact with the organism.
- Lymph nodes are enlarged bilaterally.

HISTOPATHOLOGIC FEATURES

- Primary syphilis: Skin and mucosal lesions show a perivascular and perijunctional infiltrate of lymphocytes, plasma cells and macrophages.

- At times, capillary endothelial proliferation and subsequent obliteration of small blood vessels may be appreciable. Focal erosion or ulceration is common.

SECONDARY SYPHILIS

- The symptoms of secondary syphilis usually appear about six to eight weeks after the appearance of the primary infection.
- Symptoms include fever, malaise, rash, anorexia, arthralgias and generalized painless lymphadenopathy.
- Renal, hepatic and ophthalmologic manifestations may be present.
- Meningitis occurs in 30 percent of patients with secondary syphilis but may be asymptomatic. Symptomatic aseptic meningitis occurs in one to two percent of patients and is characterized by headache, stiff neck, nausea and vomiting. It is characterized by skin lesions, mucosal lesions and lymphadenopathy.
- The oral lesions in this stage are called “*mucous patches*” that are seen over tongue, gingiva, tonsils, larynx, pharynx and cheek.
- Multiple mucous patches in the oral cavity coalesce together and form “*snail track*” like ulcers.
- It is a highly contagious stage.

HISTOPATHOLOGIC FEATURES (FIG. 13.14)

- Secondary syphilis: Skin lesions are typified by a “lichenoid-psoriasiform” configuration with a perijunctional infiltrate of lymphocytes, histiocytes and plasmacytes. Often the histiocytic component of the infiltrate is prominent and thus the biopsy may assume a “lichenoid-granulomatous” configuration.

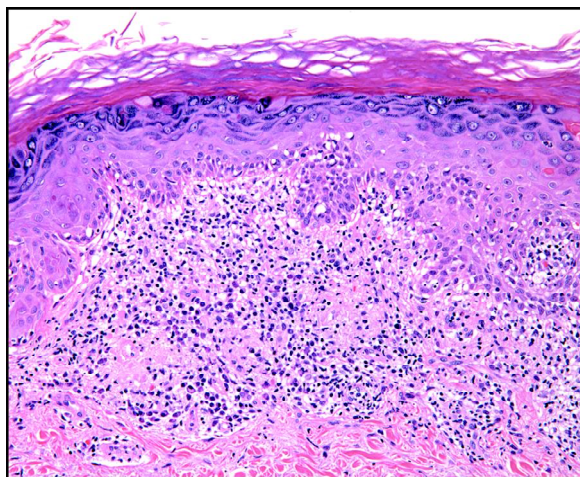


FIGURE 13.14: Histopathologic picture of secondary syphilis showing a lichenoid infiltrate, vacuolar alteration of the superjacent epithelium and subjunctional infiltrate rich in histiocytes and plasmacytes

- Small numbers of neutrophils may be included in the perijunctional infiltrate and neutrophils may also be present in an expanded overlying stratum corneum. Organisms are readily demonstrable using *T. pallidum* immunoperoxidase staining during the secondary stage.

TERTIARY SYPHILIS

- It occurs about 5 to 10 years after the primary infection and it affects nearly every organ of the body.
- Tertiary syphilis manifestations are divided into the following subgroups:
 - In **Benign tertiary syphilis**, gummatous lesions are found in skin and bones but rarely in other organs. Gummas are considered benign because they rarely involve vital body structures.
 - **Cardiovascular tertiary syphilis** can cause aortitis, aortic aneurysm, coronary stenosis, aortic insufficiency and myocarditis.
 - **Meningitic tertiary neurosyphilis** manifests with signs of meningitis and is differentiated from other causes of aseptic meningitis by a reactive result on a Venereal Disease Research Laboratory (VDRL) test of cerebrospinal fluid (CSF); this test is termed a ‘CSF VDRL.’
- Late neurosyphilis may present with focal neurological findings suggestive of a stroke.
- Typical lesions of Tertiary syphilis are called “*gumma*” which is a localized, chronic granulomatous lesion.
- Intraoral lesions of tertiary syphilis are seen on the hard and soft palate, lips and tongue (Fig. 13.15).
- Tongue lesions in syphilis are termed as ‘*Syphilitic glossitis*.’
- It is a non-contagious stage.

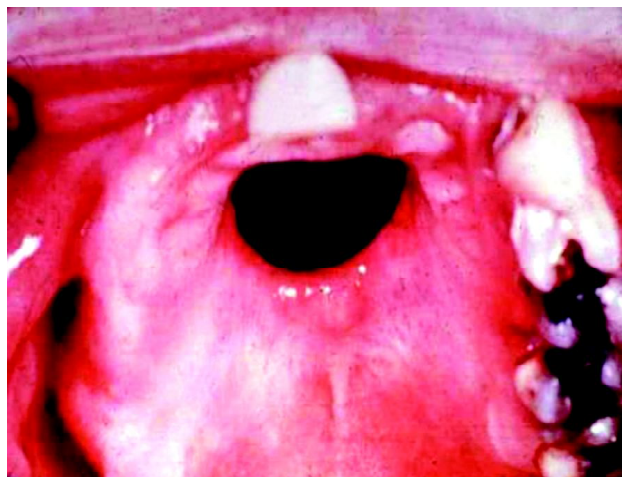


FIGURE 13.15: Tertiary syphilis causing erosion of palate

- Saddle-nose is seen due to destruction of nasal septum and collapse of nasal cartilage.

HISTOPATHOLOGIC FEATURES

- Tertiary lesions: Gummas consist of granulomatous inflammation with central necrosis flanked by plump or palisaded macrophages and fibrocytes surrounded by large numbers of mononuclear leukocytes, including many plasma cells.
- Treponemas may be scant in gummas and are sometimes difficult to demonstrate.
- Aortitis reveals inflammatory scarring of the tunica media, secondary to obliterative endarteritis of the vasa vasorum. Uneven loss of the medial elastic fibers and muscle cells may be evident.

CONGENITAL SYPHILIS

It is transmitted to the offspring only by an infected mother and is not inherited.

CLINICAL FEATURES

- It is divided into:
 - Early onset congenital syphilis
 - Late onset congenital syphilis

Early onset congenital syphilis

- Early manifestations of congenital infection vary and involve multiple organ systems. Mucous patches, rhinitis and condylomatous lesions are highly characteristic features of mucous membrane involvement in congenital syphilis.
- A diffuse maculopapular desquamative rash that involves extensive sloughing of the epithelium, particularly on the palms and soles and around the mouth and anus are common findings. These lesions are highly infectious (Fig. 13.16).
- Hepatomegaly is seen.

Late-onset congenital syphilis

- Manifestations include neurosyphilis and involvement of the teeth, bones, eyes and the eighth cranial nerve.
- The transmission usually occurs transplacentally or by sexual contact.
- Vertical transmission of early syphilis during pregnancy results in a congenital infection in at least 50 to 80 percent of exposed neonates.
- Other modes of transmission include contact with contaminated blood or infected tissues.
- Children encounter two forms of syphilis: acquired syphilis, which is almost exclusively transmitted by sexual contact and congenital syphilis, which results from transplacental transmission of spirochetes.



FIGURE 13.16: A diffuse maculopapular desquamative rash involving extensive sloughing of the epithelium



FIGURE 13.17: Screwdriver shaped maxillary central incisors in congenital syphilis

- Oral manifestations show presence of '**mulberry molars**' with constricted and atrophic cusps, '**screwdriver shaped**' incisors (Fig. 13.17).
- **Rhagades**, i.e. fissuring and scarring of corners of mouth may be seen.
- **Frontal bossae and saddle nose** are the characteristic features in infants suffering from syphilis.
- **Hutchinson's triad** of hypoplasia of incisors and molar teeth, eighth nerve deafness and interstitial keratitis in eyes is seen.

DIAGNOSIS

Diagnosis is based on detection of bacteria in smear by dark ground illumination microscopy, bacterial culture in artificial media and serological tests like Venereal Disease Research Laboratory (VDRL), Fluorescent treponemal antibody (FTA), Rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay.

Management

1. Primary, secondary and early latent diseases are treated with a single intramuscular (IM) dose of benzathine penicillin G (50,000 U/kg; not to exceed 2.4 million U).
2. In patients with primary syphilis, doxycycline and tetracycline have shown a high serological treatment success rate, comparable to penicillin.⁴
3. Azithromycin has also demonstrated a high cure rate in a long-term follow-up.⁵
4. Patients who are allergic to penicillin and do not have neurosyphilis and are not pregnant may be treated with either doxycycline (100 mg oral [PO] bid for 2 wk) or tetracycline (500 mg PO qid for 2 wk). Shorter-acting forms of penicillin must be used to treat neurosyphilis to produce reliably therapeutic levels in the cerebrospinal fluid (CSF).
5. Aqueous crystalline penicillin G is recommended if congenital syphilis is proved or is highly suspected. The recommended dosage is 100,000 to 150,000 U/kg/d IV every 8 to 12 hours to complete a 10-day to 14-day course. Procaine penicillin G (50,000 U/kg IM) has been recommended as an alternative to treat congenital syphilis.
6. Congenital syphilis in older infants and children is treated with aqueous crystalline penicillin (200,000–300,000 U/kg/d IV divided every 6 h for 10–14 d).
7. Syphilis in pregnancy is treated with penicillin, regardless of the stage of pregnancy. Patients are administered 3 doses of benzathine penicillin (2.4 million U IM at 1-wk intervals).
8. Erythromycin treatment for pregnant patients who are allergic to penicillin is not a reliable treatment for the fetus.
9. Early-acquired syphilis (i.e. primary, secondary, latent syphilis of < 1 y duration) is treated with a single dose of IM benzathine penicillin G in a total dose of 50,000 U/kg (not to exceed 2.4 million U).
10. Syphilis greater than 1 year duration is treated with benzathine penicillin G, 50,000 U/kg IM (not to exceed 2.4 million U) weekly for three successive weeks.
11. The recommended treatment for neurosyphilis is aqueous crystalline penicillin G (200,000–300,000 U/kg/d IM [50,000 U/kg every 4–6 h]) for 10 to 14 days (adult dose, 12–24 million U/d [2–4 million U every 4 h]), followed by a single dose of benzathine penicillin (50,000 U/kg/dose, not to exceed 2.4 million U) in 3 weekly doses.
12. Surgical correction of facial defects gives good esthetic results.
13. Correction of dental defects using veneers or partial or full coverage crowns may be done.

ACTINOMYCOSIS

Actinomycosis is a chronic granulomatous, suppurative and fibrosing disease. The causative microorganisms, actinomyces, are related to mycobacteria and corynebacteria. Traditionally they are considered as a transition between bacteria and fungi. They are gram-positive, non-motile, non-sporing, non-capsulated filaments called as '*ray fungus*' (Fig. 13.18).

Bollinger, 1877, for the first time found a mould like organism in a lesion of lumpy jaw in cattle.⁶ Later, **Wolff and Israel, 1891**, isolated an anaerobic bacillus from human lesions.⁷ This was named *Actinomyces israelii*. The actinomyces species is present as a commensal in mouth, intestine and vagina.

ETIOPATHOGENESIS

- *Actinomyces israelii*, *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Actinomyces viscosus* and *Actinomyces meyeri* most frequently cause human actinomycosis. *Actinomyces gerencseriae* may also cause disease in humans.
- According to the Center for Disease Control and Prevention (CDC), three former coryneform bacteria now have been added to the *Actinomyces* group and are thought to be potential causes for disease; these include *Actinomyces neuui*,⁸ *Actinomyces radingae* and *Actinomyces turicensis*.
- *Actinomyces radidentis*, a recently described species, has been isolated with polymerase chain reaction from patients with endodontic infections.⁹
- Predisposing factors for *Actinomyces* infection include:
 - Poor dental hygiene
 - Oral surgical procedures
 - Dental treatment

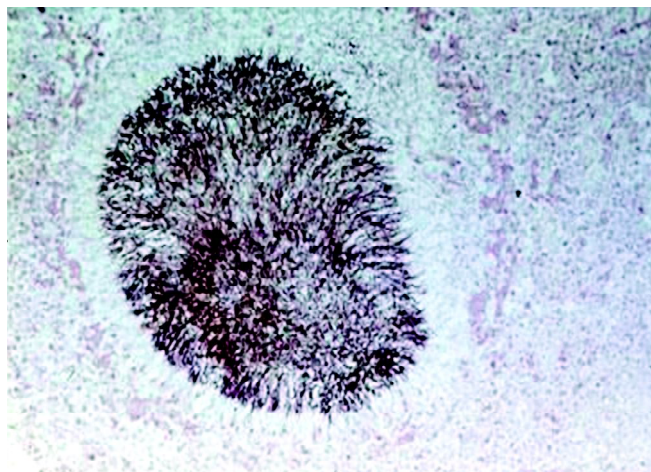


FIGURE 13.18: Actinomyces 'Ray fungus'

- Oral trauma
- Chronic mastoiditis
- Chronic otitis
- Chronic tonsillitis
- Any risk factor for aspiration
- Alcohol or drug intoxication
- Altered mental status
- Neurologically devastated patients
- Previous gastrointestinal surgery
- Perforation of the bowel, appendix, or colon
- Abdominal trauma
- Foreign bodies
- Typhoid fever
- Amoebic dysentery
- Prior *Actinomyces* infection at a distant site, such as lungs, abdomen, or pelvis
- Extension from contiguous source, such as cervicofacial actinomycosis, paranasal infection or middle ear infection
- Prolonged use of intrauterine contraceptive devices
- Spread from intestinal infection.

CLINICAL FEATURES

- Infection can develop in individuals of all ages
- More commonly seen in males as compared to females
- Usual pattern of disease is abscess formation which drains by sinus tracts
- In human beings, infection occurs in four clinical forms.

Cervicofacial actinomycosis

- This is the most common and recognized presentation of the disease.
- *Actinomyces* species are commonly present in high concentrations in tonsillar crypts and gingivodental crevices. Many patients have a history of poor dentition, oral surgery or dental procedures, or trauma to the oral cavity.
- Chronic tonsillitis, mastoiditis and otitis are also important risk factors for actinomycosis.
- Periostitis or osteomyelitis can develop if the infection extends to facial and maxillary bones. The mandible appears to be one of the most common osteomyelitis sites.
- Meningitis can also develop if the process extends into the cranial bones through sinus tracts.
- Patients may present with an acute form of the disease characterized by the formation of a painful pyogenic abscess with trismus and fistulas that drain the characteristic sulfur containing granules.
- More commonly, patients present with a painless indurated mass at the angle of the jaw or submandibular region with one or several draining sinus tracts that discharge sulfur granules.

Thoracic actinomycosis

- The most common route for infection is aspiration of oropharyngeal or gastrointestinal secretions.
- Patients may have a history or risk factors for aspiration.
- Other less common routes of infection include extensions from cervicofacial disease or spread from the abdomen and rarely, dissemination through blood from other sites of infection.
- The most common clinical presentation is a chronic, indolent, slowly progressing pneumonia with or without pleural involvement. Patients present with a productive cough, fever, chest pain and weight loss. The condition can mimic tuberculosis or malignancy.
- The disease can spread to the mediastinum and cause tracheoesophageal fistulas, pericarditis, myocarditis or endocarditis.
- Posterior mediastinal involvement can lead to vertebral infection with bone destruction or disease of paraspinal muscles and soft tissues.
- Specific clinical or radiologic findings are not recognized.
- Physical examination reveals diffuse rales and rhonchi. Decreased breath sounds can be appreciated if a pleural empyema is present.
- The patient appears chronically ill.
- Radiographic findings have the appearance of pneumonitis or a mass lesion and frequently, a pleural effusion is present.
- Hilar adenopathy can often be observed.
- Extension to adjacent tissues with involvement of chest wall muscles and soft tissues may lead to the formation of sinus tracts extending to the skin. This finding should always raise the possibility of actinomycosis.

Abdominal actinomycosis

- Abdominal actinomycosis is the most covert and indolent of all forms of the disease.
- Diagnosis is rarely suspected or made on clinical grounds. Usually, the laboratory or the pathologist provides the diagnosis.
- The infection usually develops after gastrointestinal mucosal integrity is broken from surgical procedures or trauma, although, on many occasions, the inciting conditions may not be apparent.
- Conditions such as typhoid fever, amoebic dysentery and the presence of foreign bodies, such as chicken and fish bones, have precluded the development of actinomycosis.
- Appendicitis with perforation is the most common predisposing event and as a result, right-sided abdominal infection is far more common than left-sided abdominal infection. The inciting event can precede the diagnosis by months to years.
- Patients present with nonspecific symptoms and findings, such as fever, weight loss, diarrhea or constipation and abdominal pain. Extension to the perirectal space is not uncommon and these patients present with defecation symptoms.
- Hepatic, renal and splenic disseminations are uncommon complications of abdominal actinomycosis.

- An abscess or a hard, firm mass fixed to underlying tissue can be palpated in all abdominal quadrants, more commonly in the right lower quadrant.
- Sinus tracts that extend to the abdominal wall or perirectal tissues may be found sporadically. Patient experiences localized or diffuse abdominal tenderness.
- Hepatomegaly and jaundice can be found with liver involvement. Appearance of symptoms is indolent and the patient may have had symptoms for months before seeking attention.

Pelvic actinomycosis

- This condition is extremely rare in the pediatric population and is almost exclusively observed in patients who present with prolonged use of intrauterine contraception devices, usually for longer than two years.
- Pelvic actinomycosis may develop from extension of intestinal infection, commonly from indolent ileocecal disease.
- Patients present with an indolent history of vaginal discharge, abdominal or pelvic pain, menorrhagia, fever, weight loss and prolonged use of an intrauterine contraceptive device.
- Upon physical examination, a pelvic mass can be felt on the adenexa and a vaginal or cervical discharge can be observed with speculum examination.

A fifth variety has been found recently that involves the central nervous system.

CNS disease

- Clinical features are indistinguishable from those of other infections of the CNS.
- The findings in patients without meningeal involvement are typically those of a space-occupying lesion with focal neurologic defects and increased intracranial pressure.
- The specific signs and symptoms are attributed to the anatomic location of the abscess, empyema or actinomycoma.
- Patients with chronic meningitis have an indolent picture that is no different from other chronic meningitides with headaches, low toxicity and subtle neurologic findings dominating the picture.

HISTOPATHOLOGIC FEATURES

- Pus from the lesion when examined on a clean slide shows sulfur granules
- Central area shows abscess within which colonies of microorganisms are seen
- Colonies appear to be floating in a sea of neutrophils associated with multinucleated giant cells and macrophages.

DIAGNOSIS

- Clinical features in a patient
- Demonstration of organism in tissue section or smear
- Culture of tissue section or smear.

Management

1. Surgery is indicated for resection of necrotic tissue, debulking of large masses, sinus tract excision, incision and drainage of empyemas and abscesses and bone curettage.
2. Surgery alone is not curative and the use of prolonged courses of antibiotics is always required.
3. For most complicated cases, 4 to 6 weeks of intravenous penicillin G followed by 6 to 12 months of oral penicillin V is indicated. For patients with penicillin allergy, clindamycin, ceftriaxone, chloramphenicol and tetracyclines are good alternatives.
4. Parenteral and oral combinations of these drugs have been successful. Because co-infection with *A. actinomycetemcomitans* is common, antibiotic cover for this organism when present is important, especially in patients who are critically ill.
5. Actinomycosis is susceptible to third-generation cephalosporins, rifampin, trimethoprim-sulfamethoxazole, ciprofloxacin, tetracyclines and chloramphenicol.

NOMA

Noma or cancrum oris is a rapidly spreading, gangrenous stomatitis occurring in debilitated or nutritionally deficient persons. Predisposing factors such as infections like diphtheria, dysentery, measles, syphilis, tuberculosis, blood dyscrasias, etc. may play an important role in development of this condition. The microorganisms responsible for this condition are thought to be fusospirochetal as seen in acute necrotizing ulcerative gingivitis, which are followed by streptococci, staphylococci and diphtheria bacilli.

CLINICAL FEATURES

- It occurs mostly in children who are malnourished, but may also be seen in adults
- The lesion begins as a small ulcer on gingival mucosa and spreads rapidly involving the surrounding tissues.
- The tissues become inflamed, necrotic and finally a demarcation is seen between the normal and the pathologic tissues (Fig. 13.19)
- Fever, malaise, nausea are common symptoms
- Foul odor from oral cavity is evident
- If left untreated, patient may die of toxemia.

Management

1. Maintenance of proper nutrition is the prime aim to prevent this condition.
2. The prognosis is better if antibiotics are administered before the patient reaches the final stages.



FIGURE 13.19: Noma showing necrosis of the skin on the cheeks

TETANUS

The word tetanus comes from the Greek *tēnos*, which is derived from the term *teinein*, meaning to stretch. Nicolaier discovered the anaerobic bacillus *Clostridium tetani* in 1885.¹⁰ In 1889, Koch's pupil, Kitasato, obtained the bacillus of tetanus in pure culture and associated the disease to animals.¹⁰

CLASSIFICATION

There are four clinical types of tetanus, viz:

1. Generalized
2. Localized
3. Cephalic
4. Neonatal.

Approximately 50 to 75 percent of patients with **generalized tetanus** present with trismus secondary to masseter muscle spasm. Nuchal rigidity and dysphagia also are early complaints that cause *risus sardonicus*, the ironic smile of tetanus, resulting from facial muscle involvement. As the disease progresses, patients have generalized muscle rigidity with intermittent reflex spasms in response to stimuli (i.e. noise, touch). Tonic contractions cause opisthotonus (i.e. flexion and adduction of the arms, clenching of the fists and extension of the lower extremities). During these episodes, patients have intact sensorium and feel severe pain. The spasms can cause fractures, tendon ruptures and acute respiratory failure.

Patients with **localized tetanus** present with persistent rigidity in the muscle group close to the injury site. The muscular rigidity is caused by a dysfunction in the interneurons that inhibit the alpha motor neurons of the affected muscles. No further CNS involvement occurs and this form has very low mortality rates.

Cephalic tetanus is uncommon and usually occurs following head trauma or otitis media. Patients with this form

present with cranial nerve palsies. The infection may be localized or may become generalized.

Neonatal tetanus is a major cause of infant mortality in underdeveloped countries. Infection results from cord contamination during unsanitary delivery conditions, coupled with a lack of maternal immunization. At the end of the first week of life, infected infants become irritable, feed poorly and develop rigidity with spasms. This form of tetanus has a very poor prognosis for survival.

ETIOPATHOGENESIS

- Tetanus results from infection with *C. tetani*, a motile, spore-forming, anaerobic, gram-positive bacillus. This bacillus is found in or on soil, manure, dust, clothing, skin and 10 to 25 percent of human gastrointestinal tracts. The spores need tissue with the proper anaerobic conditions to germinate; the ideal media are wounds with tissue necrosis.
- Under anaerobic conditions, the spores of *C. tetani* germinate and produce two toxins: tetanolysin (a hemolysin with no recognized pathologic activity) and tetanospasmin, which is responsible for tetanus. These toxins bind irreversibly to the axon terminals. The spores give the bacilli a '**drumstick appearance**' (Fig. 13.20).
- Once the toxin is synthesized, it moves from the contaminated site to the spinal cord in 2 to 14 days. When the toxin reaches the spinal cord, localized or cephalic tetanus may occur initially, followed by generalized tetanus.

CLINICAL FEATURES

- Neonatal tetanus accounts for 50 percent of the tetanus-related deaths in developing countries.
- It may occur at any age.
- Common first signs of tetanus are headache and muscular stiffness in the jaw (i.e. lockjaw), followed by neck stiffness,

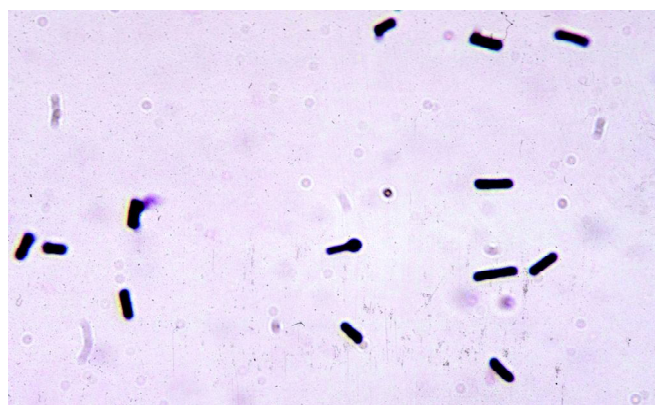


FIGURE 13.20: *Clostridium tetani* showing a 'drumstick appearance'

difficulty in swallowing, rigidity of abdominal muscles, spasms and sweating.

- Patients often are afebrile.
- Severe tetanus results in opisthotonos, flexion of the arms, extension of the legs, periods of apnea resulting from spasm of the intercostal muscles and diaphragm and rigidity of the abdominal wall (Fig. 13.21).
- Late in the disease, autonomic dysfunction develops, with hypertension and tachycardia alternating with hypotension and bradycardia.

Management

1. Passive immunization with human tetanus immune globulin (TIG) shortens the course of tetanus and may lessen its severity. A dose of 500 U appears as effective as larger doses.
2. Supportive therapy may include ventilatory support and pharmacologic agents that treat reflex muscle spasms, rigidity and tetanic seizures.
3. Benzodiazepines have emerged as the mainstay of symptomatic therapy for tetanus. To prevent spasms that last longer than 5 to 10 seconds, administer diazepam intravenously, typically 10 to 40 mg every 1 to 8 hours. Vecuronium (by continuous infusion) or pancuronium (by intermittent injection) are adequate alternatives.
4. Penicillin G, which has been used widely for years, is not the drug of choice. Metronidazole (e.g. 0.5g q6h) has comparable or better antimicrobial activity and penicillin is a known antagonist of GABA, as is tetanus toxin.
5. Physicians also use sedative hypnotics, narcotics, inhalational anesthetics, neuromuscular blocking agents and centrally acting muscle relaxants (e.g. intrathecal baclofen).
6. To date, reports indicate that more than 26 adults with severe tetanus have been treated with intrathecal baclofen. A representative dose of the continuous infusion is 1750 mcg per day. Case reports and small case series outline the efficacy of intrathecal baclofen in controlling muscle rigidity. The effects of baclofen begin within 1 to 2 hours and persist for 12 to 48 hours. The half-life elimination of baclofen in CSF ranges from 0.9-5 hours. After lumbar intrathecal administration, the cervical-to-lumbar concentration ratio is 1:4. The major adverse effect of baclofen is a depressed level of consciousness (LOC) and respiratory compromise.

MYCOTIC INFECTIONS OF THE ORAL CAVITY

CANDIDA ALBICANS

In recent years there is an emergence of opportunistic infections caused by *Candida*. Furthermore, many resistant forms of *Candida* have emerged in the past several years. Hence, it is



FIGURE 13.21: Tetanic rigidity

important to discuss about methods of sampling and techniques currently available for identification of isolates. *Candida albicans* is a common inhabitant of the oral cavity. The thallus of *Candida* consists of yeast cells. It is an ovoid or spherical budding cell, mainly responsible for opportunistic infections like candidiasis.

CLASSIFICATION

Candidal infection is frequently classified into two types:

1. Mucocutaneous candidiasis (oral or oropharyngeal, intestinal, esophageal, etc.)
2. Systemic candidiasis (involves eyes, kidneys and other visceral organs).

ETIOLOGY

Various predisposing factors favor the development of candidiasis.

- Acute and chronic diseases like tuberculosis, diabetes mellitus and anemia
- Myxedema, hypoparathyroidism and Addison's disease
- Immunodeficiency like AIDS
- Nutritional deficiency like Fe, Vit. B6, Vit. A, etc
- Prolonged hospitalization for chronic illness, debilitating disease
- Radiation therapy
- Prolonged use of antibiotics, steroids and cytotoxic drugs.

ORAL MANIFESTATIONS

- **Acute pseudomembranous candidiasis:** This is the form most often seen in children. It occurs mainly in debilitated or chronically ill children. Oral lesions include soft, white, slightly elevated plaque occurring on buccal mucosa, tongue, gingiva and floor of the mouth called as **thrush** (Fig. 13.22). The plaques consist of masses of fungal hyphae with intermingled desquamated epithelium, keratin, fibrin, necrotic debris and leukocytes.



FIGURE 13.22: Soft, white, curd-like plaques



FIGURE 13.23: Creamy, convex colonies on Sabouraud's dextrose agar

- **Acute atrophic:** The lesions appear red or erythematous rather than white thus appearing pseudomembranous where membrane has been wiped off. It is the only type of candidiasis which is painful according to Lehner.¹¹
- **Chronic hyperplastic:** Lesion consists of white persistent plaques on lips, cheeks and tongue. It is often called as leukoplakia type of candidiasis.
- **Chronic mucocutaneous:** Presents oral lesions similar in appearance and at similar sites as chronic hyperplastic candidiasis.
- **Chronic atrophic:** Also called as denture sore mouth, a diffuse inflammation of denture bearing areas often occurring with angular cheilitis.

DIAGNOSIS

Diagnosis is usually on the basis of clinical features and culture. Various techniques for recovery of *Candida* from oral cavity are:

- Smear
- Swab
- Concentrated oral rinse
- Imprint culture
- Impression culture technique
- Salivary culture technique
- Culture media that can be used:
 - Most used is **Sabouraud's dextrose agar (Odds 1991)** which permit growth of *Candida* and suppress growth of other species of oral bacteria due to its low pH.¹² It is incubated aerobically at 37 degree celsius for 24 to 48 hours. *Candida* develops as creamy, convex colonies on Sabouraud's dextrose agar (SDA) (Fig. 13.23).
 - **Pagano-Levin agar:** Distinguishes between *Candida* species based on reduction of triphenyltetrazolium chloride.
 - **Albicans ID:** Differentiation is done on the basis of chromogenic substrate for hexoseaminidase detection.

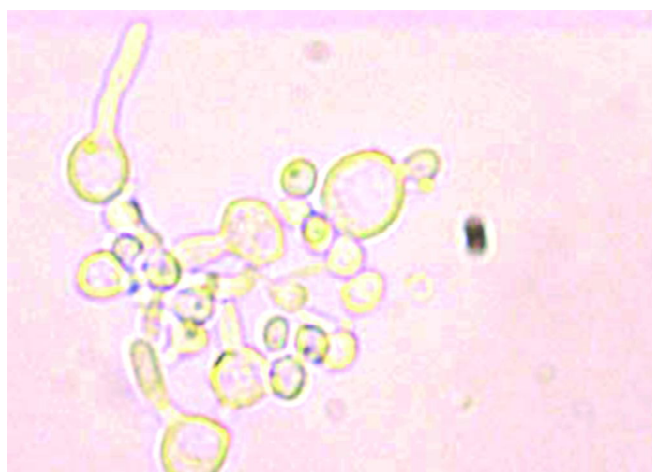


FIGURE 13.24: Germ tube formation in serum

- Method by Taschdjian et al, 1960, is the standard laboratory method for identifying *C. albicans*.¹³ Test involves induction of hyphal outgrowths from yeast cultured in serum for 2 to 4 hours at 37 degree celsius. Approximately 95 percent *C. albicans* produce germ tubes (Fig. 13.24) along with *C. stellatoidea*, *C. tropicalis* and *C. dubliniensis*.

Management

1. Improved oral hygiene is of importance which includes control of caries, keeping pacifiers and appliances clean, replacing contaminated tooth brushes.
2. Topical antifungal agents like compounded clotrimazole suspension (10 mg/ml) and nystatin oral suspension (100,000 U per ml) may be swished for 2 minutes and swallowed/expectorated four times daily for two weeks. The patient should not eat or drink for 30 minutes afterwards. Adolescents can use 1 to 2

pastilles (200,000 U) slowly dissolved in the mouth 5 times daily.

3. All antifungal agents formulated for topical use contain sweeteners and may promote caries if used for an extended period. Nystatin solution contains 30 to 50 percent of sucrose. Daily use of topical fluoride is recommended to reduce the caries potential.
4. Clotrimazole troches (10 mg) also very rich in sucrose can be used by slowly dissolving in mouth, one troch every 3 hours while awake (5 per day) for 14 days. The child must be of age and maturity to comprehend and follow instructions to use troch vehicle. Liver toxicity has been reported in patients using clotrimazole. Further clinical studies are required to establish the safety of the drug in children less than 3 years.
5. Systemic antifungal drugs are advantageous when other topically delivered medications are administered concurrently. It is usually reserved for children either not tolerating or failing topical treatment or those at risk of systemic infections.
6. Systemic agents include clotrimazole 6 mg/kg every 12 to 24 hours for 5 to 7 days; adolescents can use a 200 mg loading dose and then 100 to 200 mg once a day for about a week.
7. Ketoconazole may also be used in children at 5 to 10 mg/kg every 12 to 24 hours and in adolescents 200-400 mg every 24 hours for 5 to 7 days. It is highly effective and has the advantage of good patient compliance. Fluconazole is generally preferred over ketoconazole which has a greater risk of associated hepatotoxicity. Itraconazole and voriconazole are two additional azoles with excellent activity against *Candida*.
8. Common side effects with systemic use include nausea, vomiting, pruritis, skin rash, abdominal discomfort, headache, abnormal liver function test and drug induced hepatitis.
9. Chlorhexidine gluconate 0.12 percent can be used as antimicrobial rinse and is most useful for maintenance purposes.
10. Antifungal ointments and cream include nystatin, clotrimazole, myconazole and ketoconazole.
11. For chronic cases of angular cheilitis, Mycolog II is the best choice when applied to the corners of the mouth 3 times a day for 5 days.

VIRAL INFECTIONS OF THE ORAL CAVITY

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) typically causes an acute infectious disease characterized by the formation of blisters on the skin or mucous membranes. Tissue preferentially involved by HSV (Herpesvirus Hominis) consists of ectodermal derivatives such as skin, mucous membrane, eyes, CNS.

- Two immunologically different types of HSV are:
 1. HSV1 or HHV1
 2. HSV2 or HHV2.

PRIMARY HSV INFECTION

- The lesion occurs in patients with no prior infection with HSV1.
- Transmitted by contact with infected saliva.
- Transferred from the mouth to other parts of the body by touching the blister with fingers and then touching other areas.
- When the virus is transferred to the eye, '*ocular herpes*' may result which is painful and dangerous.
- When herpes blister forms on the fingers or the hand, the lesion is called a '*herpetic whitlow*'.

PATHOGENESIS

- HSV-1 prefers to live in the trigeminal nerve root where it causes lesions in the oral cavity and on the face.
- After infection, the virus travels to the nerves in the face (trigeminal ganglia), where it lies dormant until triggered through either stress or disease.
- While less contagious when in its dormant state, transmission is still possible with no visible symptoms.

CLINICAL FEATURES

- Primary infection occurs most often in children between two and five years of age and is usually subclinical
- In case of clinical presentation, vesicles are formed. Vesicle rupture leads to ulceration (Fig. 13.25)
- Symptoms like fever, malaise, pain, nausea, flu, aches, regional lymphadenitis are other clinical findings
- HSV lesions erupt on intraoral tissues
- They always appear on attached tissue (attached gingiva, the hard palate and the dorsal surface of the tongue)
- HSV when involves the tongue, occurs only on the ventral (top) surface and it causes red, swollen fungiform papillae.



FIGURE 13.25: Multiple ulcers on cheek and corner of mouth

HISTOPATHOLOGIC FEATURES

- Lesional area shows an intraepidermal vesicle containing ballooned, acantholytic keratinocytes in which there are intranuclear inclusion bodies (Fig. 13.26).

DIAGNOSIS

- Diagnosis is based on clinical history, HSV isolation by culture and by examining antibody titer in serum of the patients.

Management

1. Symptomatic treatment is often provided to facilitate intake of nutrition and relief from pain.
2. Prevention of dehydration is of utmost importance in children.
3. Acyclovir [9-(2-hydroxyethoxymethyl) guanine] if used early is found to be effective.
4. Vidarabine (adenine arabinoside) and Idoxuridine (5-iodo-2'-deoxyuridine) are also being used as specific antiviral chemotherapeutic agents.
5. Healthy and nutritional diet can help boost the body's natural ability to control the disease.

COMPLICATIONS

- Eczema herpeticum
- Corneal scarring and permanent damage to eyesight
- Encephalitis.

RECURRENT HSV INFECTION

- Usually seen in adult patients and manifests clinically as an attenuated form of primary disease
- Vesicles precede ulcers. Ulcers are multiple and confluent
- Occurs in keratinized mucosa.

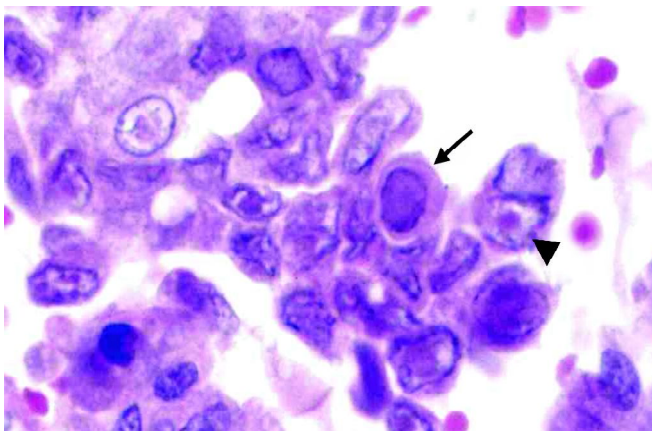


FIGURE 13.26: Histopathologic picture of herpes simplex showing viral cytopathic effect with both Cowdry type A (arrowhead) and Cowdry type B (short arrow) inclusions

PATHOGENESIS

- Reactivation of latent HSV 1
- Triggers include physical trauma, sunlight, stress and immunosuppression.

CLINICAL FEATURES

- Affects perioral skin, lips, gingiva, palate
- Self-limiting entity
- Lesion is preceded by tingling and burning sensation and feeling of tautness, swelling or slight soreness and subsequent development of vesicle
- Edema at the site of the lesion is common occurrence.

Management

1. Symptomatic treatment is often provided to facilitate intake of nutrition and relief from pain.
2. Possible control with Acyclovir.
3. Systemic treatment is superior to topical treatment.

HERPES ZOSTER

Herpes zoster is an acute vesicular inflammation characterized by inflammation of dorsal root ganglia, or extramedullary cranial nerve ganglia. It is associated with vesicular eruptions of the skin or mucus membrane in areas supplied by the affected sensory nerves.

ETIOLOGY

Primary infection by varicella-zoster virus results clinically in chicken pox, while a recurrent infection results clinically in herpes zoster (shingles).

CLINICAL FEATURES

- Chicken pox is more common in childhood whereas herpes zoster lesions are more common in adult life (Fig. 13.27).
- Occurs with equal frequency in males and females.
- Herpes zoster (shingles) is usually diagnosed by the distribution of the rash it causes.
- The distribution of the rash always corresponds to the distribution of a single major nerve branch.
- The distribution of the rash usually involves exactly one half of one of the cervical or thoracic dermatomes, wrapping from the midline of the back, around to the midline on the front of the body.
- When the infection involves the lumbar or sacral dermatomes, the rash involves only one of the affected limbs.
- Shingles (herpes zoster) is not considered to be contagious.
- This is because a healthy person who is exposed to a person suffering from an active shingles infection will not contract shingles.



FIGURE 13.27: Chickenpox presenting as rashes on the skin

- On the other hand, he or she may become infected with chickenpox if he/she has never been inoculated against it, either by having had chickenpox during childhood, or being inoculated with the vaccine.
- The first symptom is usually one-sided pain, tingling, or burning.
- The pain and burning may be severe.
- Red patches on the skin form, followed by small blisters that look very similar to early chickenpox.
- The blisters break, forming small ulcers that begin to dry and form crusts. The crusts fall off in two to three weeks.
- Additional symptoms may include:
 - Abdominal pain
 - Chills
 - Difficulty moving some of the muscles of the face
 - Ptosis
 - Fever
 - General ill-feeling
 - Genital lesions
 - Headache
 - Hearing loss
 - Joint pain
 - Loss of eye motion (ophthalmoplegia)
 - Swollen glands (lymph nodes)
 - Taste problems
 - Vision problems.

HISTOPATHOLOGIC FEATURES

The histopathology of this lesion shows ballooning degeneration of the epithelial cells (Fig. 13.28).

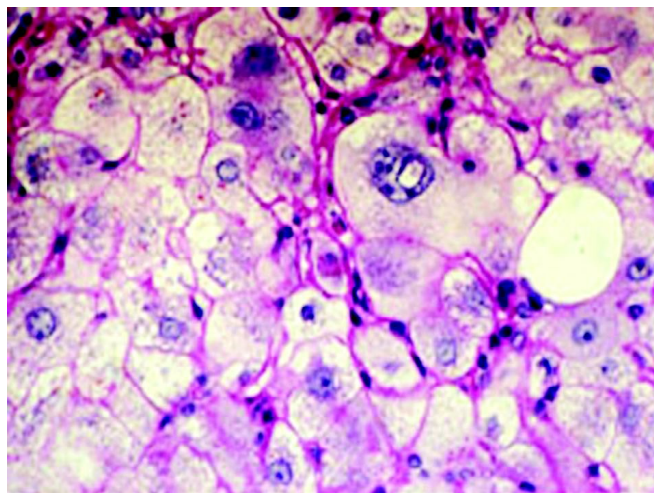


FIGURE 13.28: Ballooning degeneration in epithelial cells

Management

1. Acyclovir is the treatment of choice.
2. Corticosteroids may be used with caution as clinical course is more severe in immunocompromised patients.
3. Antihistamines may be used to reduce itching.
4. Skin should be kept clean, and contaminated items should not be reused.

SMALLPOX

Smallpox is also called as 'variola'. **Farr** first accurately predicted variola infection rates in the 1830s. Once the disease and its method of spread were understood better, smallpox vaccination became mandatory in developed countries in the early 1900s. On December 9, 1979, the WHO global commission for certification of small pox declared that smallpox eradication has been achieved throughout the world (Fig. 13.29).¹⁴ Hence, discussion of smallpox here is fortunately only of historical interest.

Variola is a member of the orthopoxvirus genus, of which cowpox, monkeypox, orf and molluscum contagiosum also are members. Poxviruses are the largest animal viruses, larger than some bacteria. They have a large genome, composed of 200 kilobase (kb) double-stranded DNA enclosed in a double membrane layer. Poxviruses are the only viruses that can replicate in cell cytoplasm without the need of a nucleus (Fig. 13.30).

The virus is acquired from inhalation, although virus particles can remain viable on fomites (clothing, bedding, surfaces) for approximately one week. The virus initially

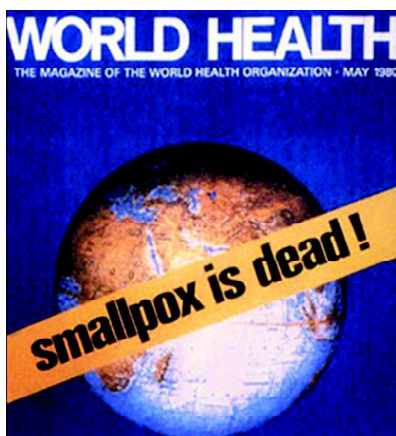


FIGURE 13.29: Declaration of eradication of smallpox



FIGURE 13.31: Multiple small, elevated, yellowish green pustules

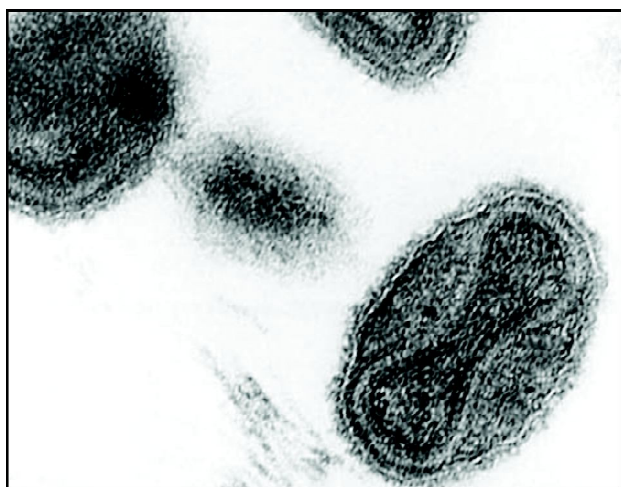


FIGURE 13.30: Variola viruses

replicates in respiratory tract epithelial cells. From there, a massive asymptomatic viremia ensues, resulting in focal infection of the skin, intestines, lungs, kidneys, and brain. The multiplication in the skin epithelial cells first leads to a rash, progressing into deep-seated pustules approximately 14 days after inoculation (Fig. 13.31). A cell-mediated immune response is responsible for pustule formation, as immunocompromised rabbits do not produce these characteristic lesions. Patients who survive an initial infection often have severely deformed skin from the pustules and subsequent granulation tissue formation.

Currently, the clinical diagnosis of smallpox is based on several criteria. The major criteria are: (1) a febrile prodrome 1 to 4 days before rash onset; (2) the classic smallpox lesions (i.e. deep-seated, firm, round, well-circumscribed lesions); and (3) lesions that are at the same stage of development.

The minor criteria include (1) a centrifugal distribution of lesions, with the first lesions on the oral mucosa or palate, face, or forearms; (2) a toxic or moribund appearance; (3) the slow evolution of lesions of 1 to 2 days per stage; and (4) lesions that appear on the palms and soles.¹⁵

Management

1. Immediate contact and droplet isolation of the patient is required.
2. The patient and any individual who came into contact with the patient up to 17 days prior to the illness (including the treating physician and nursing staff) should remain in isolation until a definite diagnosis is made. Presently, this requires sending a viral culture to the CDC in Atlanta.
3. The most likely scenario of a variola outbreak is from a terrorist attack. Given the highly infective nature of the organism (not taking into account a genetically altered virus), researchers estimate that 1 infected patient can subsequently infect 20 new contacts during the infectious stage of the illness.
4. The presentation of a clinically apparent case implies that a larger population has probably been infected.
5. Because of the medicolegal and social implications of quarantine and isolation for a minimum of 17 days, coordinated involvement on the federal, state and local levels is mandatory. In practicality, a strict quarantine of a large segment of the population is probably not possible.
6. Once the disease is fully manifested, medical treatment of variola is supportive care. Vaccinations and postexposure interventions are the mainstays of treatment. The various vaccines available and being tested are divided into generations. First-generation

vaccines are composed of vaccinia virus derived from calf lymph or chicken embryos, have little attenuation and represent the majority of the vaccine stockpile. Second-generation vaccines are viruses taken from first-generation vaccines that are then sterilely tissue-cultured with the aim of decreasing adverse outcomes. Lastly, third-generation vaccines use replication-deficient viruses that are highly attenuated, again with the aim of decreasing side effects and adverse outcomes.

7. The vaccinia (smallpox) vaccine and vaccinia immune globulin (VIG) are available only through the CDC and state and federal health agencies. Dryvax, and now ACAM200, are the only vaccines available, although vaccines from other countries may be made available in a smallpox outbreak.

MEASLES (RUBEOLA)

Measles is an infection produced by a paramyxovirus. Until late 1980s, when a vaccine was produced against this infection, children used to suffer from measles very commonly.

CLINICAL FEATURES

- Most of the cases occur during spring and spread through respiratory droplets
- Incubation period is from 10 to 12 days
- Prodromal symptoms of fever, malaise, coryza, conjunctivitis and cough occur
- Initial lesion occurs as a rash on the face, trunk and extremities lasting for four to seven days. Rash is replaced by brown pigmentation
- Oral manifestations occur in the form of **Koplik's spots** which occur as small, bluish to white macules on buccal and labial mucosa and less often on soft palate
- These pathognomonic spots represent foci of epithelial necrosis and have been described as "**grains of salt**" on a red background
- Other manifestations include:
 - Pitted enamel hypoplasia of developing permanent teeth
 - Enlargement of accessory lymphoid tissues.

HISTOPATHOLOGIC FEATURES

- Initially **Koplik's spots** represent areas of focal hyperparakeratosis, epithelial spongiosis, intercellular edema, dyskeratosis and epithelial syncytial giant cells
- As the spot ages, epithelium exhibits exocytosis by neutrophils leading to microabscess formation, necrosis and ulceration
- Within the hyperplastic lymphoid tissue, there are numerous multinucleated giant lymphocytes termed as **Warthin-Finkeldey giant cells**.

Management

1. Since the complication rate is high, the best line of management for measles is vaccination — MMR (mumps, measles, rubella).
2. Routine vaccination is recommended for all children between the ages of 12 and 15 months with a second dose administered between the ages of 4 and 6 years.
3. In healthy patients, fluids and non-aspirin antipyretics are recommended for symptomatic relief.

COMPLICATIONS

Otitis, pneumonia, persistent bronchitis, diarrhea and subacute sclerosing panencephalitis.

RUBELLA (GERMAN MEASLES)

Rubella is a mild viral infection caused by Toga virus. Its importance lies in its capacity to induce birth defects in the developing fetus. In the past, this infection occurred in cycles, with localized epidemics every 6 to 9 years and pandemics every 10 to 30 years. An effective vaccine, first released in 1969, is now used widely and has dramatically affected the epidemiology of the infection and broken the cycle of occurrences.

ETIOLOGY

- Rubella is caused by toga virus (RNA virus) (Fig. 13.32)
- Infection is transmitted by droplets as the virus is present in throat infections.
- Congenital rubella results from transmission of virus from infected mother to the fetus through transplacental route

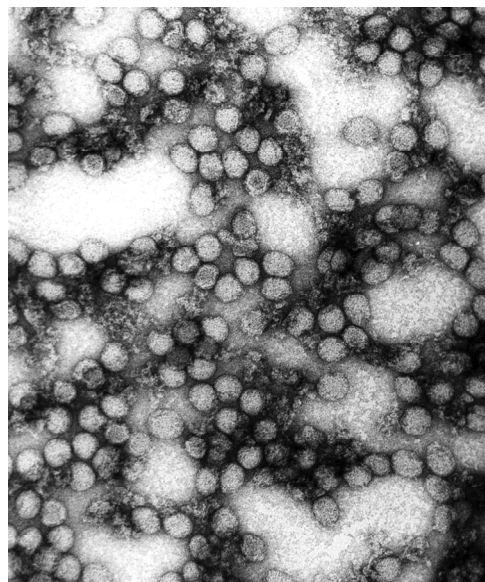


FIGURE 13.32: Toga virus

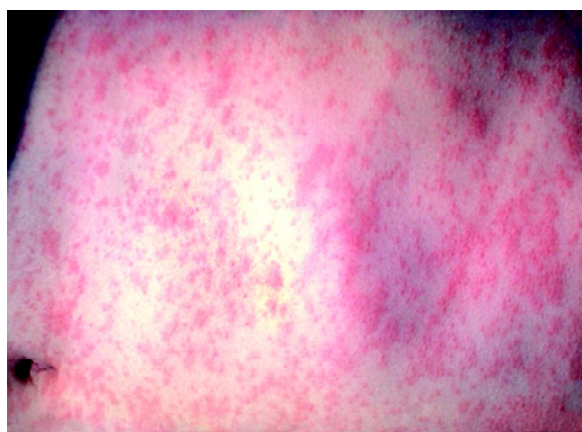


FIGURE 13.33: Rash with pink macules

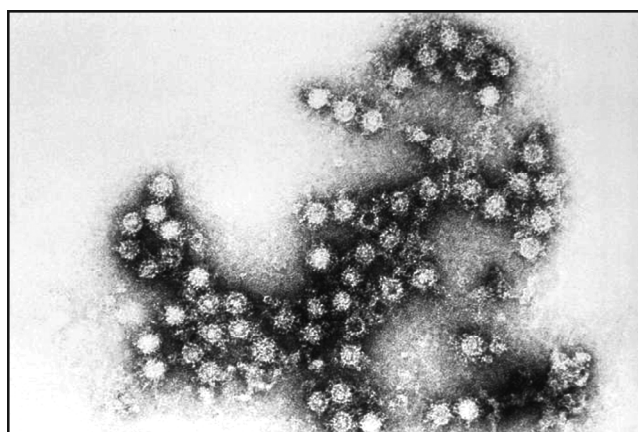


FIGURE 13.34: Coxsackievirus

and fetus is/may be associated with congenital abnormalities of eyes, heart and may cause retardation

- Acquired rubella infection affects older children and young adults
- The incubation period is 18 days.

CLINICAL FEATURES

- Malaise, headache, fever, mild conjunctivitis and lymphadenopathy.
- The rash develops within 1 to 5 days of symptom onset, starting on the face and forehead and spreading caudally to involve the trunk and extremities (Fig. 13.33).
- Lymphadenopathy may be present particularly in the posterior auricular, posterior cervical, and suboccipital chains.
- The rash consists of pink macules and papules, which may become confluent, resulting in a scarlatiniform eruption.
- Petechiae of the soft palate, known as the **Forchheimer sign**, may be present.

DIAGNOSIS

Diagnosis is based on virus isolation and serological tests.

Management

1. No antiviral therapy for rubella is available. Treatment is supportive.
2. The goals of pharmacotherapy are to reduce morbidity and prevent complications.
3. Antipyretics may be used to decrease fever.
4. Antihistamines may be used to control itching.
5. Prevention is carried out by Rubella vaccine that should be given to all children at the age of 15 months (MMR vaccine). Second dose is given at the age of 11 to 13 years. The vaccine is contraindicated in the following groups:

- Pregnant women
- Immunodeficient patients
- Patients with acute febrile illnesses
- Patients with a known allergy to components of the vaccine.

HERPANGINA

Herpangina is an acute febrile illness associated with small vesicular or ulcerative lesions on the posterior oropharyngeal structures. Herpangina typically occurs during the summer and usually develops in children, occasionally occurring in young adults.

ETIOLOGY

- Various enteroviruses cause the condition.
- Herpangina is usually caused by coxsackievirus A. Less-common causes of herpangina include coxsackievirus B, echovirus and enterovirus. Enteroviruses that cause herpangina belong to the picornaviridae family.
- Infection occurs through injection, direct contact or through droplet spread and multiple cases in a single household are common.
- Coxsackieviruses A 1-10, 16 and 22 represent the most common pathogens that cause herpangina (Fig. 13.34).
- Less-commonly, the viruses causing herpangina are coxsackievirus B 1-5, echovirus 3, 6, 9, 11, 16, 17, 22, 25, and 30 and enterovirus 71.
- Viruses that cause herpangina are typically spread via the fecal-oral route, although they may spread via the respiratory route or through fomites. Freshwater sources (e.g. lakes) may act as a reservoir for transmission.



FIGURE 13.35: Ulcers with gray base and inflamed periphery on the faucial pillars

CLINICAL FEATURES

- Herpangina is commonly seen in young children.
- It commonly occurs in summer.
- It is comparatively mild and of short duration.
- Herpangina typically has an incubation period of 7 to 14 days. Viremia occurs after inoculation and subsequently results in distant sites of infection.
- Clinical symptoms at secondary sites of infection occur after viral replication. Bilateral, anterior, cervical lymphadenopathy may occur, resulting from infection of the posterior oropharynx. Coxsackievirus A may be recovered from the nasopharynx, feces, blood, urine and cerebrospinal fluid (CSF). After clinical symptoms have resolved, asymptomatic enteroviral infection may persist in the gastrointestinal tract.
- Begins with sore throat, cough, rhinorrhea, low grade fever, headache, vomiting and abdominal pain.
- Patients soon exhibit small vesicles which rupture to form crops of ulcers with a gray base and inflamed periphery on the faucial pillars, posterior pharyngeal wall, buccal mucosa and tongue (Fig. 13.35).
- Vesicles preceding the ulcer are small and of short duration.
- Ulcers are not extremely painful.
- Erythema of the pharynx may range from mild to severe. Pharyngitis in enteroviral infections may be associated with pleurodynia, meningitis and/or exanthema.
- Bilateral, anterior, cervical lymphadenopathy may develop.

Management

Treatment is generally supportive and includes the following:

1. Hydration
2. Antipyretics (e.g. acetaminophen, ibuprofen)
3. Topical analgesics (e.g. topical lidocaine).

CYTOMEGALOVIRUS INFECTION

In 1904, Ribbert first identified histopathological evidence of cytomegalovirus, probably in tissues from a congenitally infected infant. Ribbert mistakenly assumed that the large inclusion-bearing cells he observed at autopsy were from protozoa (incorrectly named *Entamoeba mortinatalium*). **In 1920**, **Goodpasture** correctly postulated the viral etiology of these inclusions. Goodpasture used the term cytomegalia to refer to the enlarged, swollen nature of the infected cells. Human cytomegalovirus (HCMV) was first isolated in tissue culture in 1956 and the propensity of this organism to infect the salivary gland led to its initial designation as a salivary gland virus.¹⁶ In 1960, Weller designated the virus cytomegalovirus.¹⁷

During the 1970s and 1980s, knowledge of the role of cytomegalovirus as an important pathogen with diverse clinical manifestations increased steadily.¹⁸

ETIOLOGY

Cytomegalovirus is a member of a family of 8 human herpesviruses, designated as human herpesvirus 5 (HHV-5). Taxonomically, cytomegalovirus is referred to as a Betaherpesvirinae, based on its propensity to infect mononuclear cells and lymphocytes and on its molecular phylogenetic relationship to other herpesviruses. Cytomegalovirus is the largest member of the herpesvirus family, with a double-stranded DNA genome of more than 240 kbp, capable of encoding more than 200 potential protein products. The function of most of these proteins remains unclear. As with the other herpesviruses, the structure of the viral particle is that of an icosahedral capsid, surrounded by a lipid bilayer outer envelope.

CLINICAL FEATURES

- Both sexes are equally susceptible to infection and morbidity from cytomegalovirus, although only women are at risk for transplacental transmission of infection.
- Two age groups have higher rates of acquisition of infection: toddlers who attend group day care and adolescents.
- Congenital cytomegalovirus (CMV) infection: Current estimates suggest that 30,000 to 40,000 infants are born with congenital cytomegalovirus infection annually in the United States, making cytomegalovirus by far the most common and important of all congenital infections. The likelihood of congenital infection and the extent of disease in the newborn depend on maternal immune status. If primary maternal infection occurs during pregnancy, the average rate of transmission to the fetus is 40 percent; approximately 65 percent of these infants have cytomegalovirus disease at birth. With recurrent maternal infection (i.e. cytomegalovirus infection that occurs in the context of preconceptual immunity), the risk of transmission to the fetus is lower, ranging from 0.5 to 1.5 percent; most

of these infants appear normal at birth (i.e. silent infection). Hence, congenital infection may be classified as symptomatic or asymptomatic in nature.

Symptomatic congenital cytomegalovirus/Cytomegalic inclusion disease (CID)

- Approximately 10 percent of infants with congenital infection have clinical evidence of disease at birth. The most severe form of congenital CMV infection is referred to as CID.
- CID almost always occurs in women who have primary cytomegalovirus infection during pregnancy, although rare cases are described in women with preexisting immunity who presumably have reactivation of infection during pregnancy.
- CID is characterized by intrauterine growth retardation, hepatosplenomegaly, hematological abnormalities (particularly thrombocytopenia) and various cutaneous manifestations, including petechiae and purpura (i.e. blueberry muffin baby). However, the most significant manifestations of CID involve the CNS. Microcephaly, ventriculomegaly, cerebral atrophy, chorioretinitis and sensorineural hearing loss are the most common neurological consequences of CID.
- Intracerebral calcifications typically demonstrate a periventricular distribution and are commonly encountered using CT scanning. The finding of intracranial calcifications is predictive of cognitive and audiologic deficits in later life and predicts a poor neurodevelopmental prognosis.
- Most infants who survive symptomatic CID have significant long-term neurological and neurodevelopmental sequelae. Indeed, it has been estimated that congenital cytomegalovirus may be second only to Down syndrome as an identifiable cause of mental retardation in children.

Asymptomatic congenital cytomegalovirus

- Most infants with congenital cytomegalovirus infection are born to women who have preexisting immunity to cytomegalovirus. These infants appear clinically healthy at birth; however, although infants with congenital cytomegalovirus infection appear well, they may have subtle growth retardation compared to uninfected infants. Although asymptomatic at birth, these infants, nevertheless, are at risk for neurodevelopmental sequelae.
- The major consequence of inapparent congenital cytomegalovirus infection is sensorineural hearing loss. Approximately 15 percent of these infants will have unilateral or bilateral deafness. Routine newborn audiologic screening may not detect cases of cytomegalovirus—associated hearing loss because this deficit may develop months or even years after birth.
- **Acquired cytomegalovirus infection:** In contrast to congenital infection, acquired cytomegalovirus infection

occurs postnatally. Primary infection in this context is generally asymptomatic, although cytomegalovirus disease may occur in certain risk groups as follows:

Perinatal infection

- Perinatal acquisition of cytomegalovirus usually occurs secondary to exposure to infected secretions in the birth canal or via breastfeeding. Most infections are asymptomatic. Indeed, in some reviews, cytomegalovirus acquired through breast milk has been referred to as a form of natural immunization.
- Some infants who acquire cytomegalovirus infection perinatally may have signs and symptoms of disease, including lymphadenopathy, hepatitis and pneumonitis, which may be severe. Disease secondary to acquisition by breast milk is generally limited to premature infants with low birth weight. These infants may suffer considerable morbidity. Whether interventions, such as freezing or pasteurization, are warranted to decrease the risk of transmission to these high-risk infants is unclear. More studies of long-term neurodevelopmental outcomes of premature infants who acquire cytomegalovirus infection perinatally from breast milk are needed.

Cytomegalovirus mononucleosis

- Typical cytomegalovirus mononucleosis is a disease found in young adults. Although cytomegalovirus mononucleosis may be acquired by blood transfusion or organ transplantation, cytomegalovirus mononucleosis is usually acquired via person-to-person transmission.
- The hallmark symptoms of cytomegalovirus mononucleosis are fever and severe malaise. An atypical lymphocytosis and mild elevation of liver enzymes are present.
- Clinically differentiating cytomegalovirus mononucleosis from Epstein-Barr virus (EBV)—induced mononucleosis may be difficult. Cytomegalovirus mononucleosis is typically associated with less pharyngitis and less splenomegaly. As with EBV mononucleosis, the use of -lactam antibiotics in association with cytomegalovirus mononucleosis may precipitate a generalized morbilliform rash.

Transfusion-acquired cytomegalovirus infection

- Post-transfusion cytomegalovirus infection has a presentation similar to that of cytomegalovirus mononucleosis. Incubation periods range from 20 to 60 days.
- The use of seronegative blood donors, frozen deglycerolized blood, or leukocyte-depleted blood can decrease the likelihood of transmission and is recommended for high-risk patients (e.g. neonates, immunocompromised patients).

Cytomegalovirus infections in immunocompromised patients

Cytomegalovirus causes various clinical syndromes in immunocompromised patients. Disease manifestations vary in severity depending on the degree of host immunosuppression. Infection may occur because of reactivation of latent viral infection or may be newly acquired via organ or bone marrow transplant from a seropositive donor. Infections may also be mixed in nature, with donor and recipient isolates both present. Viral dissemination leads to multiple organ system involvement, with the most important clinical manifestations consisting of pneumonitis, gastrointestinal disease and retinitis.

Cytomegalovirus pneumonitis

- Cytomegalovirus is a major cause of pneumonitis in immunosuppressed children and adults. This disease may be observed in the setting of HIV infection, congenital immunodeficiency, malignancy and solid organ or bone marrow transplant.
- The mortality rate is based on the degree of immunosuppression, with mortality rates of at least 90 percent reported in bone marrow transplant recipients. Solid organ transplant recipients are at risk of developing cytomegalovirus pneumonitis also, although mortality rates are lower.
- The illness usually begins one to three months following transplantation and starts with symptoms of fever and dry, nonproductive cough. The illness progresses quickly with retractions, dyspnea, and hypoxia becoming prominent.
- The illness is an interstitial pneumonitis, with a radiographic appearance of diffuse bilateral interstitial infiltrates. Because the differential diagnosis of pneumonitis is extensive in immunocompromised patients, consider performing a bronchoalveolar lavage or open lung biopsy to confirm the diagnosis and direct appropriate therapy.

Cytomegalovirus gastrointestinal (GI) disease

- GI tract disease caused by cytomegalovirus can include esophagitis, gastritis, gastroenteritis, pyloric obstruction, hepatitis, pancreatitis, colitis and cholecystitis. Characteristic signs and symptoms may include nausea, vomiting, dysphagia, epigastric pain, icterus and watery diarrhea.
- Stool may be hemoccult positive or frankly bloody. Endoscopy and biopsy are warranted and characteristic cytomegalic inclusion cells may be observed in GI endothelium or epithelium.
- Although CMV enteritis does not carry the same ominous prognosis as cytomegalovirus pneumonitis, antiviral therapy is warranted.
- Differentiating cytomegalovirus hepatitis from chronic rejection in liver transplant patients may be difficult, even with biopsy.

Cytomegalovirus retinitis

- Before the advent of highly active antiretroviral therapy (HAART) for HIV infection, cytomegalovirus retinitis was the most common cause of blindness in adult patients with acquired immunodeficiency syndrome (AIDS), with an overall lifetime prevalence of more than 90 percent.
- HIV-associated cytomegalovirus retinitis in children, in contrast to adults, has been relatively rare, probably reflecting overall differences in cytomegalovirus seroprevalence between the populations. Retinitis is less common in transplant patients.
- Cytomegalovirus produces a necrotic rapidly progressing retinitis with characteristic white perivascular infiltrate with hemorrhage (brushfire retinitis).
- Peripheral lesions may be asymptomatic and even advanced disease does not cause pain. In children, strabismus or failure to fix and follow objects may be important clues to the diagnosis.
- The disease can progress to total blindness and retinal detachment if left untreated. Cytomegalovirus chorioretinitis is also observed in symptomatic infants with congenital infection, although the disease does not usually progress to vision loss. The presence of chorioretinitis in an infant with congenital infection indicates a poor neurodevelopmental prognosis.

Other cytomegalovirus syndromes:

- Various syndromes have been attributed to cytomegalovirus infection, although cause and effect relationships are often difficult to establish.
- **Menetrier disease** is a rare disorder characterized by hyperplasia and hypertrophy of the gastric mucous glands, which results in massive enlargement of the gastric folds. Most cases appear to be cytomegalovirus associated, although the pathogenesis is unknown.
- In children with congenital HIV infection, co-infection with cytomegalovirus appears to accelerate the HIV disease progression and HIV-associated neurological disease. Accumulating evidence suggests that cytomegalovirus infection may be a cofactor in the pathogenesis of atherosclerosis. In addition, the phenomena of posttransplant vascular sclerosis and postangioplasty restenosis appear to be cytomegalovirus-induced lesions.
- The long-term health consequences of cytomegalovirus infection may include atherosclerosis, immunosenescence and an increased risk of malignancy. These associations require further study but provide a potential justification for universal vaccination of both sexes against cytomegalovirus.

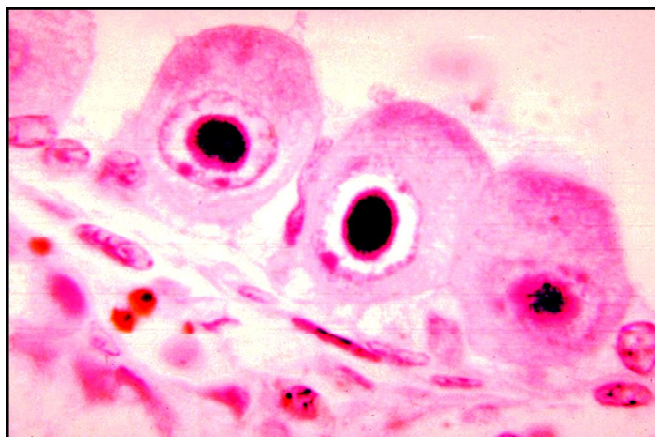


FIGURE 13.36: Histopathologic picture of cytomegalovirus inclusion bodies showing 'Owl's eye' appearance

HISTOPATHOLOGIC FEATURES

Cells infected with CMV are enlarged and have inclusion bodies which can be recognized from biopsy material. It is known as having an “owl's eye” appearance (Fig. 13.36).

Management

1. Medical care of cytomegalovirus (CMV) consists of good nutritional support, vigorous supportive care for end-organ syndromes (particularly pneumonia in immunocompromised patients) and specific antiviral therapy in select circumstances.
2. Some children with congenital cytomegalovirus require orthopedic interventions (cerebral palsy) and gastrostomy placement for enteral nutrition.
3. Nucleosides are the only true antiviral agents active against cytomegalovirus, although immunoglobulins may provide some antiviral effect, particularly in combination with these agents. These agents share a common molecular target, namely, the viral DNA polymerase. Biochemically, ganciclovir is an acyclic nucleoside analog, whereas cidofovir is an acyclic nucleoside phosphonate.
4. Ganciclovir is commonly used as preemptive therapy in transplant recipients at high risk of developing disease (e.g. a cytomegalovirus-seronegative recipient of an organ transplant from a cytomegalovirus-seropositive donor).
5. Alternatives to ganciclovir include trisodium phosphonoformate (PFA) and cidofovir. Pediatric experience with these agents is limited.

ACQUIRED IMMUNODEFICIENCY SYNDROME

The first cases of acquired immunodeficiency syndrome (AIDS) were described in the United States in 1981. At that point, the

term AIDS was not used to describe this new unexplained immune deficiency syndrome. The syndrome had several names, including “gay syndrome”, due to it being initially identified in homosexuals.¹⁹

Researchers from the Viral Oncology Unit called on the American team of Pr Gallo (National Cancer Institute, United States) who had described the only human retrovirus known at that time, HTLV 1. Pr Gallo informed them that he was also looking for the virus causing what would be known as AIDS and that he considered that it may be HTLV 1 (Human T-Cell Leukemia Virus). However, initial comparisons suggested and confirmed that this was false, particularly comparison by immunofluorescence undertaken by Marie-Thérèse Nugeyre.¹⁹

In May 1986, the International Committee on the Taxonomy of Viruses ruled that a new name, HIV (Human Immunodeficiency Virus) be given to the virus.¹⁹

Two-thirds of HIV/AIDS infections in Asia occur in India, with an estimated 5.7 million infections (estimated 3.4–9.4 million) (0.9% of population), surpassing South Africa's estimated 5.5 million (4.9–6.1 million) (11.9% of population) infections, making it the country with the highest number of HIV infections in the world. In 2005, five Indian states had high HIV/AIDS prevalence—Andhra Pradesh, Karnataka, Maharashtra, Manipur and Nagaland as did 95 districts in the states.²⁰

STRUCTURE OF HIV 1 (FIGS 13.37 AND 13.38)

The HIV-1 virus is an icosahedral, enveloped, RNA virus of the Lentivirinae subfamily of retroviruses that primarily infects human white blood cells. They are so called because their genetic material RNA must be transcribed to DNA before the virus can complete its replicative cycle. The genome of HIV contains two types of genes: the structural genes and the regulatory genes. The structural genes are responsible for direction and synthesis of proteins and glycoproteins that will give the virus its physical characteristics, i.e. shape, size, structural integrity, compartmentalization, etc. The regulatory genes are responsible for subsequent production of proteins that can affect the activities of viral components or can specifically turn other genes on and off. Among other activities, the regulatory proteins have ability to increase or decrease the replication of HIV. The activity of this regulatory gene is responsible for profound pathogenicity of HIV.²¹

Structurally, HIV is composed of two major parts: an outer envelope and inner core. The external envelope components are embedded in the lipid matrix of the membrane and are involved in the binding of the virus to the host cells during infections. The outermost viral components are arranged as spikes or knobs and extend from the lipid membrane. These external spikes are proteins with sugar molecules and are therefore glycoproteins. The core components of the virus are located internal to the outer membrane and are bound by a protein coat encompassing two

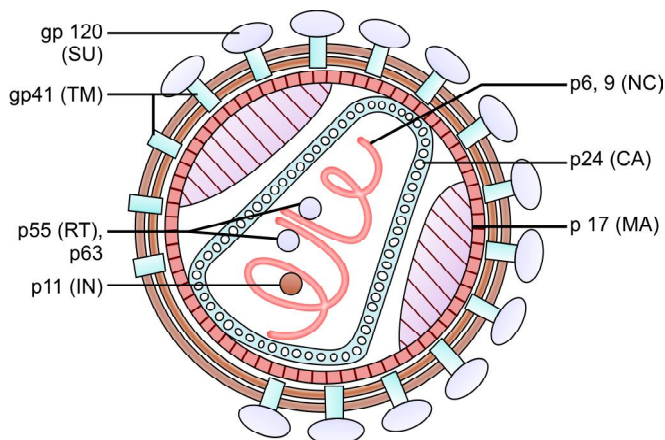


FIGURE 13.37: Structure of HIV

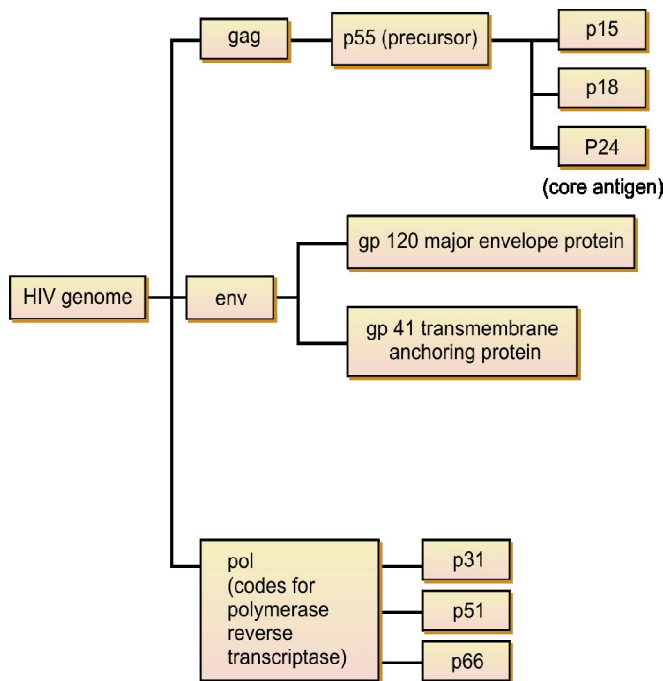


FIGURE 13.38: Genomic composition of HIV

identical copies of the nucleic acid RNA genome. Also within the core are the three viral enzymes: reverse transcriptase, integrase and protease. These enzymes are responsible for transcription, integration of the virus in the host and cleavage of other proteins respectively.²¹

The different structural antigens of HIV-1 are encoded by three major structural genes and therefore can be classified into three major groups:

1. *gag* proteins (encoded by *gag* gene, or group associated antigen gene).
2. *env* glycoproteins (encoded by the genes that determine the production of envelope components).

3. *pol* proteins (polymerase components that represents enzymes that are involved in transcription, integration and cleavage of other viral components).²¹

The most important *gag* proteins (p) are those having molecular weights of 55,000 (p55), 24,000 (p24), 17,000 or 18,000 (p17) and 15,000 Da (p15). The p55 antigen is the precursor molecule produced early in the infectious process and is eventually cleaved to produce other core proteins. All of the *gag* proteins are located in the nucleocapsid of the virus. The p17 protein lies in the matrix between the protein core and the envelope and is embedded within the internal portion of the envelope. The p24 and p15 proteins make up the core coat (capsid) that surrounds the internal nucleic acids. The major capsid component is p24.

In addition to p24, two additional core proteins, p9 and p7 which are nucleic acid binding proteins are also present. Together these proteins make-up the nucleoid core.²¹

The *env* (envelope) antigens are glycoproteins and include those components having molecular weights of 160,000 (gp 160), 120,000 (gp 120) and 41,000 Da (gp 41). The gp 160 is the precursor molecule and is not a structural component (similar to the *gag* p55); it is a component that is produced during infection, but is later cleaved to form gp120 and gp 41 (the structural envelope glycoproteins). These envelope glycoproteins contain:

1. Conserved regions (sequences constant in all HIV-1 viruses).
2. Variable regions (sequences that may vary between HIV-1 viruses).²¹

The gp41 antigen spans the inner and outer membrane of the virus and thus is often referred to as a transmembrane glycoprotein antigen. This particular antigen contains important variable regions and therefore may be specific for each type or strain of HIV-1 virus. The gp120 antigen is the major component of external envelope and is responsible for 72 knobs or spikes of the envelope. Significant variability in gp120 (as high as 15%) between the HIVs occur in the hypervariable regions of the molecule; this may be responsible for the inability of the immune system to contain the virus. Together the gp41 and gp120 antigens are involved with the fusion and attachment of HIV to the CD4 molecule on the host cells.²¹

Polymerase (*pol*) antigens include the proteins p66 (a subunit of reverse transcriptase enzyme that has RNase H activity), p51 (another subunit of reverse transcriptase enzyme), and p31 (integrase or endonuclease). Polymerase antigens are located within the core of the virus and are closely associated with the nucleic acids. Collectively, these polymerase components are responsible for:

- Conversion of viral RNA to DNA (reverse transcription)
- Integration of viral DNA into host cellular DNA

- Cleavage of precursor molecules into smaller active components; accomplished by the proteases.²¹

The precursor molecules gp160 and p55 are not structural components of the virus and are only included in the figure for completeness. These precursor components are however true gene products produced during transcription and translation. It is later but prior to virus assembly that they are cleaved to form the other structural components.²¹

Other components of virus may be antigenic and play a significant role in infection and the development of immune responses, but their exact roles are poorly understood. These viral components includes the negative regulatory proteins *nef* (p27) and *vpr* (p15), both of which may limit viral replication and the positive regulatory proteins *vpu* (p16, increases the maturation of the viral particles), *tat* (p14, transactivates gene expression), *rev* (p19, production of viral mRNA) and *vif* (p23, viral infectivity factor). Generally, these regulatory components are responsible for modifying the expression of viral proteins and for the replication of the virus. The negative regulatory factor may be responsible for limiting the degree of viral replication (down regulation), thereby leading to the latency period.²¹ Although the exact function of these regulatory factors is unknown, they play an important role in the infectious process and may govern the whole process of disease progression.²¹

REPLICATION CYCLE OF VIRUS

Refer to Figure 13.39.

CLINICAL FEATURES OF AIDS

- Disease is divided in five clinical stages:
 1. Acute HIV infection
 2. Asymptomatic/latent infection
 3. Persistent generalized lymphadenopathy
 4. AIDS related complex
 5. Full blown AIDS.

World Health Organization (WHO) classification

- Presence of 2 major signs and 1 minor sign:
 - Major signs: weight loss > 10 percent of body weight, chronic diarrhea > 1 month, prolonged fever > 1 month
 - Minor signs: persistent cough > 1 month, oral candidiasis, herpes zoster infection, persistent generalized lymphadenopathy, other opportunistic infections.

Center for Disease Control (CDC) Atlanta Classification²²

Classification is based on:

- Etiologic agent
- Natural history
- Clinical manifestation and
- CD4 T-cell counts.

AIDS is divided into three phases:

- **Early acute phase:** Level of plasma viremia, CD8 count, CD4 count, sore throat, fever, etc.
- **Middle chronic phase:** Seen after seroconversion stage, viral replication in lymphoid tissue in early stage but in late stage, patient asymptomatic.
- **Final crisis phase:** CD4 count < 200/ l, fever > 1 month, weight loss, chronic diarrhea > 1 month, opportunistic infections, aseptic meningitis, viral encephalitis, etc.

ORAL MANIFESTATIONS OF AIDS

Usually precede the general or systemic manifestations thus they are of utmost importance for a dental professional.

CLASSIFICATION

Most widely accepted European Commission Clearinghouse (**EC Clearinghouse**) classification based on:²³

- Clinical observation of the lesions and
- Are a result of special investigations for absolute diagnosis.

Divided into three broad groups:

(In Adults)

- **Group 1:** Lesions strongly associated with the HIV infection
- **Group 2:** Lesions less commonly associated with the HIV infection
- **Group 3:** Lesions seen in the HIV infection.

(In Children)

- **Group 1:** Lesions commonly associated with the HIV infection in children
- **Group 2:** Lesions less commonly associated with the HIV infection in children
- **Group 3:** Lesions strongly associated with HIV infection but rare in children.

Group 1 (Adults): Lesions strongly associated with the HIV infection in adults:

- Candidiasis: Erythematous, pseudomembranous, angular cheilitis
- Hairy leukoplakia
- Kaposi sarcoma
- Non-Hodgkin's lymphoma
- Periodontal disease: Linear gingival erythema, necrotizing gingivitis, necrotizing periodontitis.

Group 2 (Adults): Lesions less commonly associated with the HIV infection in adults:

- Tuberculosis
- Melanotic hyperpigmentation
- Necrotizing stomatitis
- Salivary gland disease

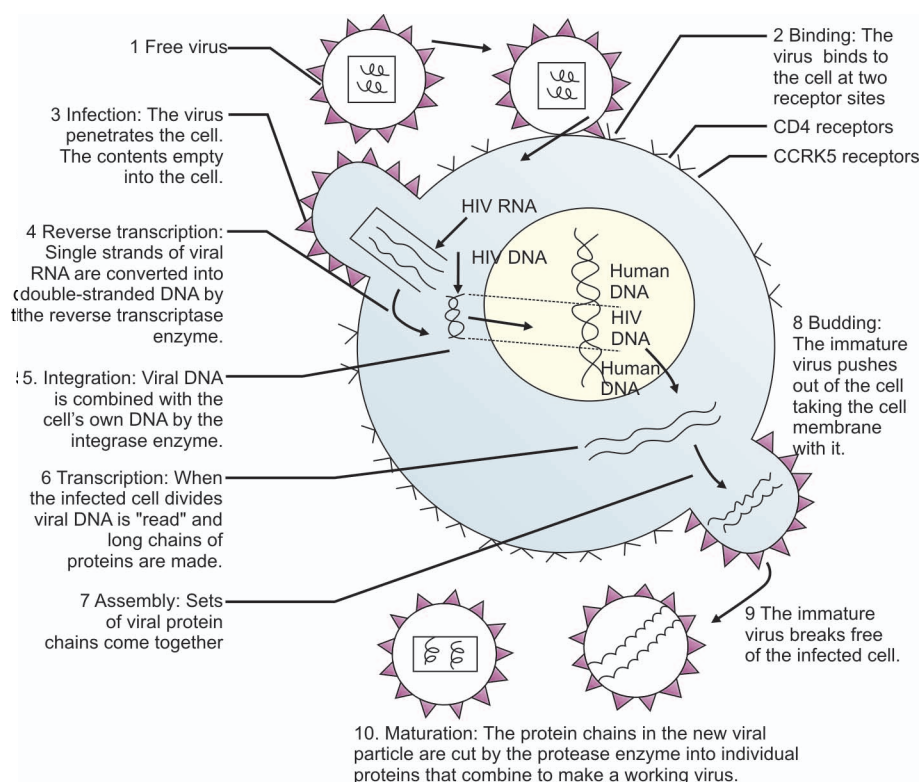


FIGURE 13.39: Replication cycle of virus

- Thrombocytopenic purpura
- Ulceration not otherwise specified
- Herpes simplex
- Human papilloma virus
- Varicella zoster virus

Group 3 (Adults): Lesions seen in the HIV infection in adults:

- Bacterial infections: *A. israelii*, *E. coli*, *Klebsiella pneumoniae*
- Drug reactions: Ulcerative erythema multiforme, lichenoid reaction
- Fungal infections: *Cryptococcus neoformans*, *Histoplasma capsulatum*
- Neurologic disturbances: Facial palsy, trigeminal neuralgia
- Recurrent aphthous stomatitis
- Viral infections: Cytomegalovirus, molluscum contagiosum.

Group 1 (Children): Lesions commonly associated with the HIV infection in children:

- Candidiasis: Erythematous, pseudomembranous, angular cheilitis
- Linear gingival erythema
- Herpes simplex
- Salivary gland disease
- Recurrent aphthous stomatitis.

Group 2 (Children): Lesions less commonly associated with the HIV infection in children:

- Bacterial infections: *A. israelii*, *E. coli*, *Klebsiella pneumoniae*
- Periodontal disease: Necrotizing gingivitis, necrotizing periodontitis
- Xerostomia
- Seborrheic dermatitis
- Viral infections: Cytomegalovirus, molluscum contagiosum, human papillomavirus, varicella-zoster virus.

Group 3 (Children): Lesions strongly associated with HIV infection but rare in children:

- Hairy leukoplakia
- Kaposi sarcoma
- Non-Hodgkin's lymphoma
- Tuberculosis related ulcers.

GROUP 1 LESIONS

1. **Candidiasis** (Fig. 13.40): Oral candidiasis is most commonly associated with *Candida albicans*, although other species, such as *C. glabrata* and *C. tropicalis*, are frequently part of the normal oral flora. A number of factors predispose patients to develop candidiasis: infancy, old age,



FIGURE 13.40: Oral thrush



FIGURE 13.41: Angular cheilitis

antibiotic therapy, steroid and other immunosuppressive drugs, xerostomia, anemia, endocrine disorders and primary and acquired immunodeficiency. Candidiasis is a common finding in people with HIV infection. Reports describe oral candidiasis during the acute stage of HIV infection, but it occurs most commonly with falling CD4⁺ T-cell count in middle and late stages of HIV disease.²⁴

The clinical appearances of oral candidiasis vary. The most common presentations include pseudomembranous and erythematous candidiasis, which are equally predictive of the development of AIDS,²⁵ and angular cheilitis. These lesions may be associated with a variety of symptoms, including a burning mouth, problems eating spicy food and changes in taste. All three of these common forms may appear in one individual.

2. **Erythematous Candidiasis:** Erythematous candidiasis appears as flat, red patches of varying size. It commonly occurs on the palate and the dorsal surface of the tongue. Erythematous candidiasis is frequently subtle in appearance and clinicians may easily overlook lesions, which may persist for several weeks if untreated.
3. **Angular Cheilitis** (Fig. 13.41): Angular cheilitis appears clinically as redness, ulceration and fissuring, either unilaterally or bilaterally at the corners of the mouth. It can appear alone or in conjunction with another form of candidiasis.

Diagnosis

Candida is a commensal organism in the oral cavity.

- Candidiasis is diagnosed by its clinical appearance and by detection of organisms on smears. Smears taken from clinical lesions are examined using potassium hydroxide (KOH), PAS, or Gram's stain. Smears are taken by gently drawing a wooden tongue depressor across the lesion. The specimen is then transferred into a drop of KOH on a glass

slide and protected by a cover slip. The smear is examined under the microscope and *Candida* is detected by finding hyphae and blastospores. Hyphae and spores are only seen in smears from lesions and are rarely seen in the healthy individual in the carrier state.

- Cultures are grown on specific media, such as Sabouraud's agar; they may be positive and yet reveal very low colony counts. This probably represents a carrier state rather than active infection. Culture is useful for establishing the *Candida* species but may not be useful for diagnosis.

Management

1. Oral candidiasis may be treated either topically or systemically. Treatment should be maintained for 7 days. Response to treatment is often good; oral lesions and symptoms may disappear in a fairly short period (ranging from 2 to 5 days), but relapses are common because of the underlying immunodeficiency. As with other causes of oral candidiasis, recurrences are common if the underlying problem persists.
2. **Topical Treatment:** Topical treatments are preferred because they limit systemic absorption, but the effectiveness depends entirely on patient compliance. Topical medications require that the patient hold medications in the mouth for 20 to 30 minutes. If the patient uses formulations containing sweetening agents for long periods, consider as concurrent treatment daily fluoride rinses (e.g. ACT or Fluorigard, available as over-the-counter preparations) for one minute once a day to be then expectorated.
3. Clotrimazole is an effective topical treatment (one oral troche [10-mg tablet]) when dissolved in the mouth five times daily. Used less frequently, one vaginal troche can be dissolved in the mouth daily. Nystatin preparations include a suspension, a vaginal tablet

and an oral pastille. Regimens are nystatin vaginal tablets (one tablet, 100,000 units, dissolved in the mouth three times a day), or nystatin oral pastille (available as a 200,000-unit oral pastille, one or two pastilles dissolved slowly in the mouth five times a day). Nystatin suspension has a high sugar content and cannot be held in the mouth long enough to be effective. Topical creams and ointments containing nystatin, ketoconazole, or clotrimazole may be useful in treating angular cheilitis. Another therapeutic choice is amphotericin B (0.1 mg/ml). Five to 10 ml of oral solution is used as a rinse and then expectorated three to four times daily.

4. Systemic Treatment: Several agents are effective for systemic treatment. Ketoconazole (Nizoral) is a 200-mg tablet taken with food once daily. Patient compliance is usually good. Careful monitoring of liver function is necessary for long-term use because of reported side effects, including hepatotoxicity. Lack of efficacy of ketoconazole may occur because of poor absorption in those with an abnormally high gastric pH.
5. Fluconazole (Diflucan) is a triazole antifungal agent effective in treating candidiasis (100-mg tablet taken once daily for 2 weeks). Several studies suggest fluconazole is effective as a prophylactic agent, although the most effective prophylaxis dosing regimen is still unclear.²⁶ Numerous reports however, describe oral and esophageal candidiasis failing to respond to treatment with fluconazole and in some of these cases investigators isolated resistant strains.²⁷ Itraconazole (100-mg capsules) may be used for the treatment of oral candidiasis (200 mg daily orally for 14 days). Itraconazole oral suspension is now available (200 mg daily for 2 weeks). Salivary levels of itraconazole are maintained for several hours after administration.
6. Ketoconazole, fluconazole, and itraconazole may interact with other medications including rifampicin, phenytoin, cyclosporin A, terfenadine, digoxin, coumarin-like medications and oral hypoglycemic medications.

Herpes Simplex (Fig. 13.42)

Herpes simplex causes both primary and secondary or recurrent disease in the oral cavity. Primary herpetic gingivostomatitis commonly occurs in children and young adults and may be followed by frequent recurrences. Following the primary episode, the virus becomes latent in the trigeminal ganglion. Recurrent oral herpes occurs at any age extraorally or intraorally.

CLINICAL FEATURES

Recurrent herpes labialis occurs on the vermillion border of the lips. The patient may report a history of itching or pain, followed by the appearance of small vesicles. These rupture

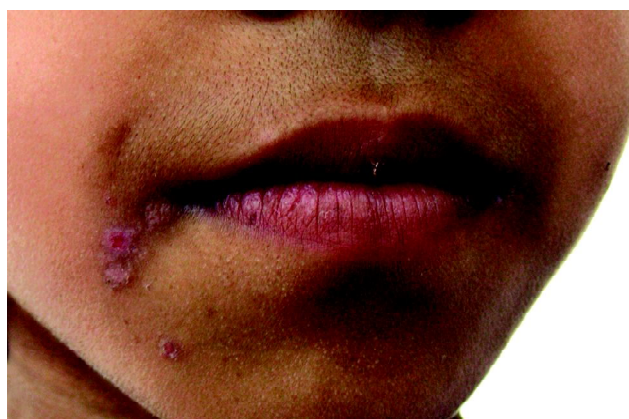


FIGURE 13.42: Resolving herpetic lesions

and form crusts. Recurrent intraoral herpes appears as clusters of painful small vesicles that rupture and ulcerate and usually heal within 1 week to 10 days. The lesions usually occur on the keratinized mucosa, such as the hard palate and gingiva, although lesions may arise on the dorsal surface of the tongue.

DIFFERENTIAL DIAGNOSIS

Rising antibody titers from initial and convalescent sera confirm primary herpetic gingivostomatitis. Examining smears of lesions (treated with Papanicolaou stain) for multinucleated giant cells confirms recurrent herpes. It is possible to demonstrate herpes simplex type 1 or type 2 by applying monoclonal antibodies to smears from the lesions (the Syva Kit, Syva Corporation, Palo Alto, CA).²⁸ Swabs taken from fluid-filled vesicles may grow herpes simplex in culture if vesicles are a few days or less old. Clinicians can distinguish between recurrent intraoral herpes simplex lesions, which always occur on keratinized mucosa (such as the hard palate and gingiva) and recurrent aphthous ulcers, which always appear on nonkeratinized mucosa. Recurrent intraoral herpes may appear more frequently in HIV-infected patients. The lesions may be painful and slow to heal.

Management

1. No treatment will permanently eradicate oral herpes simplex infections, but acyclovir may shorten the healing time for individual episodes. The optimum oral dosage of acyclovir is 1000 to 1600 mg daily for 7 to 10 days.
2. Topical acyclovir is not useful for treating intraoral lesions and may not be effective for lesions on the lips. Recurrent outbreaks of acyclovir-resistant herpes have been reported, including a case involving the facial skin, lips, nose, and mouth. In this case, the lesions resolved after treatment with foscarnet. Phosphonoformate may also prove effective.

Linear Erythematous Gingivitis

This entity appears as a 1 to 3 mm band of marginal gingival erythema, often with petechiae. It is typically associated with no symptoms or only mild gingival bleeding and mild pain. Histological examination fails to reveal any significant inflammatory response, suggesting that the lesions represent an incomplete (aborted) inflammatory response, principally with only hyperemia present. There is no evidence to suggest that this entity will proceed to the far more destructive necrotizing periodontitis. Unlike conventional gingivitis, the erythema often persists following simple dental prophylaxis. Oral rinsing with chlorhexidine gluconate 0.12 percent often reduces or eliminates the erythema and typically requires prophylactic use to avoid recurrence.

Clinicians should refer patients to a periodontist or dentist for management. The following protocol has achieved reasonable success: plaque removal, local debridement, irrigation with povidone-iodine, scaling and root planing and maintenance with a chlorhexidine mouth rinse (Peridex-R) once or twice daily. Studies show that the addition of chlorhexidine to this regimen produces significant improvement in periodontal condition.

Parotid Gland Disease

HIV infection is associated with parotid gland disease, characterized clinically by gland enlargement and diminished flow and histologically by lymphoepithelial infiltration and benign cyst formation. The enlargement typically involves the tail of the parotid gland or, less commonly, the submandibular gland and it may present uni- or bi-laterally with periods of increased or decreased size. While the appearance may raise suspicion of malignancy (salivary gland or lymphoma) or infection, aspiration of a yellow mucinous secretion supports the diagnosis of HIV-related salivary gland disease, thus avoiding unnecessary biopsy or imaging diagnostics. Occasional swelling can be managed simply by repeated aspiration and rarely is radical removal of the gland necessary. The pathophysiological mechanism is not known, though cytomegalovirus has been suggested to play a role.

Oral Ulceration

Oral ulcers resembling recurrent aphthous ulcers (RAUs) in HIV-infected persons are reported with increasing frequency. The cause of these ulcers is unknown. Proposed causes include stress and unidentified infectious agents. In HIV-infected patients, the ulcers are well circumscribed with erythematous margins. The ulcers of the minor RAU type may appear as solitary lesions of about 0.5 to 1.0 cm. The herpetiform type appears as clusters of small ulcers (1-2 mm), usually on the

soft palate and oropharynx. The major RAU type appears as extremely large (2-4 cm) necrotic ulcers. The major RAUs are very painful and may persist for several weeks.

DIAGNOSIS

The ulcers may present a diagnostic problem. Herpetiform RAUs may resemble the lesions of coxsackievirus infection, and major RAUs may require biopsy to exclude malignancy, such as lymphoma, or opportunistic infection, such as histoplasmosis. The ulcers usually occur on nonkeratinized mucosa; this characteristic differentiates them from those caused by herpes simplex.

Management

The RAU type ulcers usually respond well to topical steroids such as fluocinonide (0.05%) ointment mixed with equal parts Orabase applied six times daily or clobetasol (0.05%) ointment mixed with equal parts Orabase applied three times per day. Dexamethasone elixir (0.5 mg/5 ml) used as a mouth rinse and then expectorated two to three times daily is helpful for multiple ulcers and for those where topical ointments are hard to apply.²⁹ For HIV-infected persons with oral and gastrointestinal aphthous-like ulcers, systemic steroid therapy (prednisone 40 to 60 mg/day for 7 to 10 days) has been reported as helpful. The risks of steroid therapy, however, must be considered before administration to individuals in this population. Thalidomide (50 to 200 mg) has been used in Europe and is the subject of clinical trials in the United States.

GROUP II LESIONS

Although isolated cases of oral infection with *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Actinomyces israelii*, *Escherichia coli* and *Mycobacterium avium intracellulare* have been reported in patients with HIV infection, the most common oral lesions associated with bacterial infection are necrotizing ulcerative gingivitis and periodontitis and much less commonly, bacillary epithelioid angiomatosis and syphilis. In the case of the periodontal infections, the bacterial flora is no different from that of a healthy individual with periodontal disease. Thus, the clinical lesion is a manifestation of the altered immune response to the pathogens.

Necrotizing Ulcerative Periodontitis (NUP)

This unique periodontal lesion is characterized by generalized deep osseous pain, significant erythema that is often associated with spontaneous bleeding and rapidly progressive destruction of the periodontal attachment and bone. The destruction is not self-limiting and can result in loss of the entire alveolar process in the involved area. This very painful associated lesion

adversely affects oral intake of food, resulting in significant and rapid weight loss. Because the periodontal microflora is no different from that seen in healthy patients, the lesion probably results from the altered immune response in HIV infection. More than 95 percent of patients with NUP have a CD4 lymphocyte count of less than 200/mm³.

Management

1. Treatment consists of rinsing twice daily with chlorhexidine gluconate 0.12 percent, metronidazole (250 mg orally four times daily for 10 days) and periodontal debridement, which is performed after antibiotic therapy has been initiated.
2. Within 36 to 48 hours of antibiotic therapy, relief of pain associated with NUP is obtained.

Bacillary Epithelioid Angiomatosis (BEA)

This recently described lesion appears to be unique to HIV infection and is often clinically indistinguishable from oral Kaposi's sarcoma (KS). Since both may present as an erythematous, soft mass which may bleed upon gentle manipulation, biopsy and histological examination are required to distinguish BEA from KS. The presumed etiological pathogen, *Rochalimaea henselae*, can be identified using Warthin-Starry staining. Both KS and BEA are histologically characterized by atypical vascular channels, extravasated red blood cells and inflammatory cells. However, prominent spindle cells and mitotic figures occur only in KS. Erythromycin (erythromycin estolate, 500 mg 4 times daily for at least 10 days) is the treatment of choice for BEA.

Syphilis

While the prevalence of syphilis infection has risen significantly over the past decade, it is an uncommon cause of intraoral ulceration, even in HIV infection. Its appearance is no different from that observed in healthy individuals; it is a chronic, nonhealing, deep, solitary ulceration; often clinically indistinguishable from that due to tuberculosis, deep fungal infection, or malignancy. Dark field examination may demonstrate treponema. Positive reactive plasma reagin (RPR) and histological demonstration of *Treponema pallidum* is diagnostic. Patients with newly diagnosed syphilis should be referred to their physicians for evaluation and treatment; combination treatment with penicillin, erythromycin and tetracycline is the treatment of choice, the dosage and duration of treatment depending on presence or absence of neurosyphilis.

Necrotizing Stomatitis

Necrotizing stomatitis is an uncommon acute, painful ulceration which often exposes underlying bone and leads to considerable tissue destruction. This lesion may be a variant of major aphthous

ulceration, but occurs in areas overlying bone and is associated with severe immune deterioration. Unlike necrotizing ulcerative periodontitis, the lesion may occur in edentulous areas. As in major aphthous ulceration, systemic corticosteroid medication or topical steroid rinse is the treatment of choice.

Xerostomia

Xerostomia is common in HIV disease, most often as a side effect of antiviral medications or of the other antihypertensive, antidepressant, anxiolytic or analgesic medications commonly prescribed for patients with HIV infection. The oral dryness presents a significant risk factor for caries and can lead to rapid dental deterioration. Xerostomia also contributes to oral candidiasis, mucosal injury and dysphagia and is often associated with pain and reduced oral intake of food. Although several saliva substitutes exist, compliance is often poor and relief inadequate. For patients with residual salivary gland function, determined by gustatory challenge, oral pilocarpine (5 mg up to 3 times daily) often provides improved salivary flow and consistency. Oral hygiene instruction, regular maintenance and the use of prescription-strength, fluoridated dentifrice (Prevident 5000 Plus®) is essential.

Herpes Zoster

The reactivation of varicella-zoster virus (VZV) causes herpes zoster (shingles). The disease occurs in the elderly and the immunosuppressed.

Clinical features: Oral herpes zoster generally causes skin lesions. Following a prodrome of pain, multiple vesicles appear on the facial skin, lips and oral mucosa. Skin and oral lesions are frequently unilateral and follow the distribution of the maxillary and/or mandibular branches of the trigeminal nerve. The skin lesions form crusts and the oral lesions coalesce to form large ulcers. The ulcers frequently affect the gingiva, so tooth pain may be an early complaint.

Management

Acyclovir limits the duration of the lesions. For herpes zoster, the standard oral dosage is 800 mg five daily for 7 to 10 days, which is considerably higher than that recommended for treatment of herpes simplex.

Molluscum Contagiosum (Fig. 13.43)

Molluscum contagiosum (MC) is a common, self-limiting viral disease of the skin and mucous membranes. It was first described by **Bateman in 1817**. It is caused by molluscipoxvirus, which belongs to unclassified genus of poxvirus species.

The mature virion is a brick-shaped particle measuring 150 × 350 nm. Molluscum contagiosum has a usual incubation period of 14 to 50 days, although there are reports of newborns



FIGURE 13.43: Dome shaped papule with central umbilication

having lesions as early as seven days postpartum. The lesions may persist for weeks to months suggesting that the virus provokes a minimal cell-mediated immunity.

It occurs predominantly in preadolescent children, sexually active adults, participants in sports with skin to skin contact and in individuals with impaired cellular immunity.

Although Molluscum contagiosum as a clinical entity is well-defined and commonly observed, few data regarding its epidemiology in the pediatric population exist.

CLINICAL FEATURES

According to one survey, incidence of molluscum contagiosum in India in children less than 14 years of age was found to be 2.5 percent. Immunocompromised individuals act as the ideal hosts for this lesion. Transmission factors in children are accounted by a warm and humid environment, overcrowding, poor hygiene, sharing towels, clothes, etc. These are the conditions that are usually seen in orphanages and other institutions where children reside together. In adults, Molluscum contagiosum is usually sexually transmitted.

Signs of sexual abuse should always be looked for when lesions on genitalia are present in children.

The lesions of molluscum contagiosum appear dome-shaped, flesh-colored papules, usually multiple and with central umbilicated area. The umbilicated area consists of white, waxy curd-like core.

HISTOPATHOLOGIC FEATURES

The lesional area shows inverted lobules of hyperplastic, acanthotic squamous epithelium arranged in lobulated pattern.

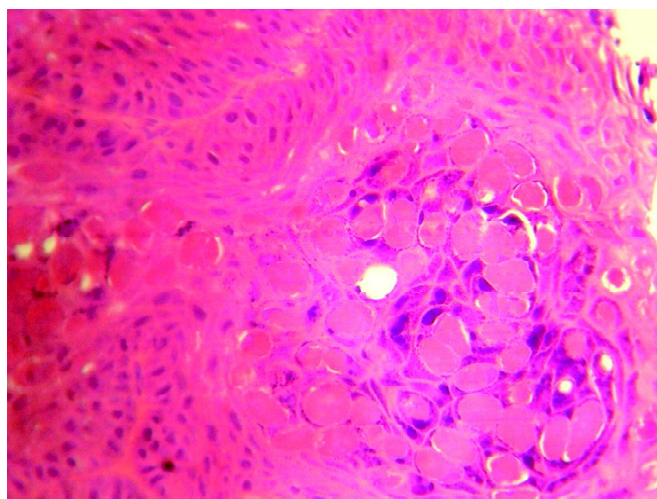


FIGURE 13.44: Histopathologic picture of molluscum contagiosum showing enlarged keratinocytes with eosinophilic 'Henderson and Paterson' inclusion bodies

The centers of these bulbous structures are filled with enlarged, altered keratinocytes with eosinophilic viral inclusions referred to as Henderson and Paterson inclusion bodies. The inclusion bodies are the result of a virally induced transformation process. Initially, the small virion particle is formed in the cytoplasm of the epithelial cells above the basal layer. These eosinophilic particles grow in size as they progress towards the granular cell layer causing compression of the nucleus to the periphery of the infected epithelial cells (Fig. 13.44).

Management

1. Molluscum contagiosum is a self-limiting disease, which, if left untreated, will eventually resolve in immunocompetent hosts but may be protracted in atopic and immunocompromised individuals. One of the most common, quick, efficient methods of treatment is cryotherapy.
2. An easy method to remove the lesions is eviscerating the core with an instrument such as a scalpel, sharp tooth pick, edge of a glass slide or any other instrument capable of removing the umbilicated core. Because of its simplicity, patients, parents and caregivers may be taught this method so that new lesions can be treated at home.
3. Curettage, use of adhesive tape, 0.05 ml of 5 percent podofilox in lactate-buffered ethanol, Cantharidin (0.9% solution of collodion and acetone), Tretinoin 0.1 percent cream, oral cimetidine, 10 percent potassium hydroxide, Imiquimod 5 percent cream, Cidofovir either topically or intralesional injection have also been used for the management of molluscum contagiosum with varying success.

Human Papillomavirus Lesions

Oral warts, papillomas, skin warts and genital warts are associated with the human papillomavirus (HPV). Lesions caused by HPV are common on the skin and mucous membranes of persons with HIV disease. Anal warts have frequently been reported among homosexual men. Because the HPV types found in oral lesions in HIV-infected persons are different from the HPV types associated with anogenital warts, clinicians should probably not use the term condyloma acuminata to describe oral HPV lesions.

CLINICAL FEATURES

HPV lesions in the oral cavity may appear as solitary or multiple nodules. They may be sessile or pedunculated and appear as multiple, smooth-surfaced raised masses resembling focal epithelial hyperplasia or as multiple, small papilliferous or cauliflower-like projections. I have identified HPV types 7, 13 and 32 have been identified in some of these oral warts.

Malignant transformation of HPV oral lesions has not been reported, but the identification of four new HPV types in these lesions warrants further study.

Cytomegalovirus

Oral ulcers caused by cytomegalovirus (CMV) have been reported. These ulcers can appear on any mucosal surface and may be confused with aphthous ulcers, necrotizing ulcerative periodontitis (NUP) and lymphoma. Unlike aphthous ulcers, however, which usually have an erythematous margin, CMV ulcers appear necrotic with a white halo. Diagnosis of CMV ulcers is made from a biopsy. Immunohistochemistry may be helpful.

CMV ulcers in the oral cavity usually occur in individuals with disseminated CMV disease. Therefore, diagnosis of CMV-infected oral ulcers should be followed by examination for the systemic disease. CMV ulcers resolve when ganciclovir is used to treat CMV disease.

GROUP III LESIONS

Hairy Leukoplakia and Epstein-Barr Virus: Oral hairy leukoplakia (HL), which presents as a nonmovable, corrugated or “hairy” white lesion on the lateral margins of the tongue, occurs in all risk groups for HIV infections, although less commonly in children than in adults. HL occurs in about 20 percent of persons with asymptomatic HIV infection and becomes more common as the CD4⁺ T-cell count falls.³⁰ No report describes HL in mucosal sites other than the mouth. HL has occurred in non-HIV-infected people including recipients of bone marrow, cardiac and renal transplants.

Hairy leukoplakia and progression of HIV disease:

Diagnosis of HL is an indication of both HIV infection and immunodeficiency; it is an indication for a work-up to evaluate and treat HIV disease. HL correlates with a statistical risk for more rapid progression of HIV disease. Those persons with hairy leukoplakia who progressed to CDC-defined AIDS most rapidly, however, were more often anergic to *Candida* antigen at diagnosis of hairy leukoplakia, indicating significant immunosuppression at that time. Progression to CDC-defined AIDS was more rapid in those HIV-infected persons with hairy leukoplakia than in those without hairy leukoplakia, even after adjustment for CD4⁺ T-cell count.

PATHOGENESIS

The Epstein-Barr virus (EBV) in hairy leukoplakia is both unusual in that deletions in the EBNA 2 gene have been described and in that to date no viral DNA is found in the basal layers of HIV. Intraepithelial Langerhans’ cells (LCs) are reduced or absent in the hairy leukoplakia lesion, which correlates with the presence of viral antigens. It is not known whether the lack of LCs is a cause of hairy leukoplakia or a consequence of EBV infection.

In electron microscopic specimens, investigators have found structures consistent with a herpes group virus. One structure consisted of 100-nm intranuclear virions and 240-nm encapsulated virus particles. Other structures are 48- to 52-nm particles visible in the suprabasal layer. Closer to specimen surfaces, where the nuclei are more condensed, arrays of these particles and herpes group particles occurred in the same cell. Several studies described the appearance of these particles in HL biopsies.

CLINICAL FEATURES

Hairy leukoplakia lesions vary in size and appearance and may be unilateral or bilateral. The surface is irregular and may have prominent folds or projections, sometimes markedly resembling hairs. Occasionally, however, some areas may be smooth and flat. Lesions occur most commonly on the lateral margins of the tongue and may spread to cover the entire dorsal surface. They may also spread downwards onto the ventral surface of the tongue, where they usually appear flat. Hairy leukoplakia lesions can also occur on the buccal mucosa, generally as flat lesions. Rarely, lesions occur on the soft palate. Hairy leukoplakia usually does not cause symptoms.

DIAGNOSIS

- Hairy leukoplakia should be diagnosed by biopsy for definitive diagnosis.

- Experienced clinicians can make a presumptive diagnosis of hairy leukoplakia in association with HIV disease from the clinical appearance, although it can be confused with oral candidiasis. The typical microscopic appearance of hairy leukoplakia includes acanthosis, marked parakeratosis with the formation of ridges and keratin projections, areas of ballooning cells and little or no inflammation in the connective tissue. The ballooning changes resemble koilocytosis. Cells are enlarged; some contain enlarged ballooning cells with pyknotic nuclei. Some contain perinuclear haloes.
- Definitive diagnosis of hairy leukoplakia requires demonstration of EBV. EBV may be readily demonstrated in biopsy specimens by a variety of techniques. Cells taken from the hairy leukoplakia lesion by scraping can be used for a noninvasive diagnosis using *in situ* hybridization.

Management

1. Hairy leukoplakia usually is asymptomatic and does not require treatment.
2. It is almost always a manifestation of HIV infection and clinicians should arrange evaluation of HIV disease and appropriate treatment for patients with hairy leukoplakia.
3. Hairy leukoplakia has disappeared in patients receiving high-dose acyclovir for herpes zoster, presumably because of the anti-EBV activity of acyclovir. Doses of acyclovir (2.5 to 3 mg per day for 2 to 3 weeks) usually eliminate HL, but the lesion usually recurs with cessation of treatment.
4. Elimination or almost complete clinical resolution of the lesion has occurred in patients treated with agents such as desciclovir, an analog of acyclovir, phosphonoformate, Retin A and podophyllin resin, although lesions tend to recur within a few months.
5. Case reports describe hairy leukoplakia disappearing during treatment with ganciclovir, zidovudine and aerosolized pentamidine. Katz and colleagues have shown that HL both appears and disappears in patients receiving zidovudine, although no case-controlled studies are available.³¹
6. Occasionally, *Candida albicans* may be found in hairy leukoplakia lesions. Treatment consists of antifungal medications.

Kaposi's Sarcoma

Kaposi's sarcoma may occur intraorally, either alone or in association with skin and disseminated lesions. Intraoral lesions have been reported at other sites and may be the first manifestation of late-stage HIV disease (AIDS). Kaposi's sarcoma occurs most commonly in men but also has been observed in women.

CLINICAL FEATURES

Kaposi's sarcoma can appear as a red, blue, or purplish lesion. It may be flat or raised solitary or multiple. The most common oral site is the hard palate, but lesions may occur on any part of the oral mucosa, including the gingiva, soft palate and buccal mucosa and in the oropharynx. Occasionally, yellowish mucosa surrounds the Kaposi's sarcoma lesion. Oral Kaposi's sarcoma lesions may enlarge, ulcerate and become infected. Good oral hygiene is essential to minimize these complications.

Management

1. Treatment is determined on the basis of the number, size and location of the oral Kaposi's sarcoma lesions. The choice of therapy depends on the effect of treatment on the adjacent mucosa, pain associated with treatment, interference with eating and speaking, and the patient's preference. It is important to perform thorough dental prophylaxis before initiating therapy for Kaposi's sarcoma lesions involving the gingiva. Response to therapy is improved if all local plaque and calculus are removed. Local application of sclerosing agents may reduce the size of oral lesions.
2. Local treatment is appropriate for large oral Kaposi's sarcoma lesions that interfere with eating and talking. Oral lesions can be treated surgically or with localized intralesional chemotherapy. Surgical removal is suitable for small, well-circumscribed lesions such as gingival or tongue lesions. Surgical removal can be performed under local anesthesia with a blade or with the carbon dioxide laser. Intralesional vinblastine is useful for treating small lesions, particularly on the palate or gingiva. Several studies have documented the effectiveness of one or two injections of 0.1 to 0.2 mg per ml solution of vinblastine. Post-treatment pain is fairly common, but systemic effects are rare. The pain usually disappears several days after therapy.
3. Radiation therapy may be indicated for large, multiple lesions. A single dose of 800 cGy or an equivalent fractionated dose is frequently used and produces a good response. Side effects include xerostomia and mucositis, although both conditions usually improve with cessation of radiation therapy.

Lymphoma

Non-Hodgkin's lymphoma is rare in the pediatric population, but when present, it is a strong indicator of HIV infection.

CLINICAL FEATURES

Diffuse, undifferentiated non-Hodgkin's lymphoma (NHL) is a frequent HIV-associated malignancy. Most are of B-cell origin and Epstein-Barr virus occurs in cells from several cases. Lymphoma can occur anywhere in the oral cavity and there

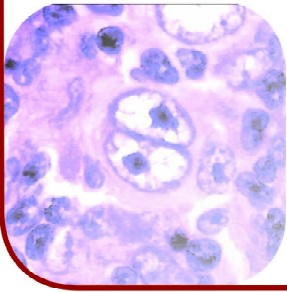
may be soft tissue involvement with or without involvement of underlying bone. The lesion may present as firm, painless swelling that may be ulcerated. Some oral lesions may appear as shallow ulcerations. Oral NHL may appear as solitary lesions with no evidence of disseminated disease.

Management

After diagnosis of the oral lesions, the patient must be referred for further evaluation of disseminated disease and its subsequent treatment.

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Hematological Disorders in Children

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CHAPTER OVERVIEW

Introduction
Classification
Anemia
Thalassemia
Hemophilia
Polycythemia
Leukocytosis
Neutrophilia
Eosinophilia

Monocytosis
Basophilia
Agranulocytosis
Neutropenia
Lymphocytosis
Leukemia
Thrombocytopenia
Lymphoma

INTRODUCTION

Fortunately, most of the hematologic diseases are often dramatic and demonstrative in the type and presentation of orofacial signs and symptoms. Recognition of these signs and symptoms is important for a clinician in order to be able to avoid any inadvertent dental mishaps.

CLASSIFICATION

Bleeding disorders can be broadly classified as those:

1. Involving the red blood cells
2. Involving the white blood cells
3. Involving blood platelets
4. Involving specific blood factors.

ANEMIA

DEFINITION

Anemia is defined as an abnormal reduction in:

- Number of circulating red blood cells.
- The quantity of hemoglobin.
- The volume of packed red cells in a given unit of blood.

CLASSIFICATION

It includes four subtypes:

1. Classification by cause of anemia
2. Classification by histologic picture
3. Effect on the circulatory system.
4. Etiologic classification by Wintrobe¹

Classification by Cause of Anemia

- Blood loss anemia
- Aplastic anemia
- Megaloblastic anemia
- Hemolytic anemia
 - Hereditary spherocytosis
 - Sickle cell anemia
 - Erythroblastosis fetalis.

Classification by Histologic Picture

- Macrocytic
- Normocytic
- Microcytic
- Hypochromic microcytic.

Effect on the Circulatory System

Etiologic Classification by Wintrobe¹

1. **Loss of blood**
 - a. Acute post hemorrhagic anemia.
 - b. Chronic post hemorrhagic anemia.
2. **Excessive destruction of red corpuscles**
 - a. Extra corpuscular causes:
 - Antibodies
 - Infection
 - Splenic sequestration and destruction
 - Associated disease states

- Drugs, chemicals and physical agents
- Trauma to RBCs.
- b. Intra corpuscular causes:
 - Hereditary
 - Disorders of glycolysis
 - Faulty synthesis or maintenance of reduced glutathione
 - Qualitative or quantitative abnormalities in synthesis of globin
 - Abnormalities of RBC membrane
 - Erythropoietic porphyria.
 - Acquired
 - Paroxysmal nocturnal hemoglobinuria
 - Lead poisoning.
- 3. **Impaired blood production resulting from deficiency of substances essential for erythropoiesis:**
 - Iron deficiency.
 - Deficiency of various B vitamins (B12, B9, B6, B3).
 - Protein deficiency.
 - Possibly ascorbic acid deficiency.
- 4. **Inadequate production of mature erythrocytes:**
 - Deficiency of erythroblasts
 - Atrophy of bone marrow: aplastic anemia
 - i. Chemical or physical agents
 - ii. Hereditary
 - iii. Idiopathic.
 - Isolated erythroblastopenia:
 - i. Thymoma
 - ii. Chemical
 - iii. Antibodies.
 - Infiltration of bone marrow
 - Leukemia, lymphomas
 - Multiple myeloma
 - Carcinoma, sarcoma
 - Myelofibrosis.
 - Endocrine abnormality
 - Myxedema
 - Addisonian adrenal insufficiency
 - Pituitary insufficiency
 - Hyperthyroidism.
 - Chronic renal disease
 - Infections
 - Non-infectious diseases including granulomatous and collagen diseases.
 - Cirrhosis of liver.

COMMON ORAL MANIFESTATIONS IN ANEMIA

- They are mainly due to changes in metabolism in the mucosal epithelium

- Dekeratinization occurs along with epithelial atrophy
- Atrophy of filiform papillae of tongue
- Ulceration and inflammation of the mucosa
- Gingivitis and periodontitis are also common
- Angular cheilitis
- Susceptible to oral monilial infections.

NUTRITIONAL DEFICIENCY

- Usually present in adolescent girls
- Exogenous iron needed during first two years of life and in adolescence
- Cracking or splitting of nails
- Painful tongue
- Decreased healing after dental surgeries
- Mucosal pallor.

FOLIC ACID DEFICIENCY ANEMIA

Folic acid deficiency anemia is a common, slowly progressive, megaloblastic anemia characterized by red blood cells that are larger than normal and hence the term macrocytic (Fig. 14.1) when referring to this type. The red blood cells are also deformed, and both their rate of production and their lifespan are diminished. Folic acid anemia occurs most often in infants, adolescents, pregnant and lactating females, alcoholics, the elderly and in those with malignant or intestinal diseases.

ETIOPATHOGENESIS

Folic acid is needed for the orderly production of deoxyribonucleic acid (DNA) in all tissue cells and is a component of three of the four DNA bases: thymine, adenine and guanine. In bone marrow, it is required for the normal production of the

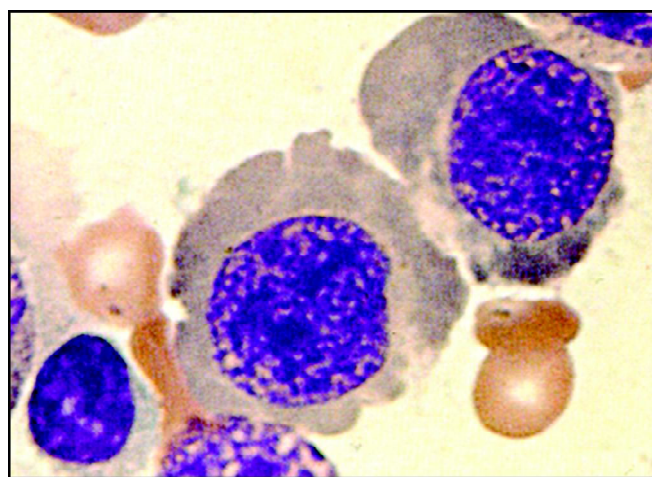


FIGURE 14.1: Folic acid deficiency anemia showing macrocytes similar to that seen in vitamin B deficiency anemia

red blood cells and for RNA synthesis. It is basically required for the formation of heme, the pigmented, iron-containing portion of the hemoglobin in erythrocytes. A deficient intake of folic acid impairs the maturation of young red blood cells, which results in anemia. Folic acid circulates through and is stored in the liver and a deficiency is almost always because of insufficient amounts in the diet.

Absorption of folic acid occurs primarily in the upper small intestine and does not depend on intrinsic factor as vitamin B12 does. A deficiency of folic acid is more common than a cobalamin (B12) deficiency. Folic acid stores are also depleted more rapidly than cobalamin stores and without proper dietary intake, a megaloblastic anemia will develop.

Folic acid deficiency anemia is common during pregnancy. Both folate and iron are essential for red cell production and during pregnancy there is an increased need to supply both the mother and the developing infant. This type of anemia is common in newborns because of the increasing survival rates of premature infants. Not only can it be a danger to the mother, but also contributes to fetal malformations. The most common birth defect resulting from a deficiency of this vitamin is spina bifida. Deficiency of folic acid is also one of the contributory factors for the development of cleft lip and/or palate. This lays emphasis on the importance of prenatal counseling.

During the 1980s, a considerable body of evidence accumulated stating that spina bifida and other neural tube defects were associated with folate deficiency. It is now widely recognized that folate supplements are necessary and best started before pregnancy occurs since closure of the neural tube occurs by day 28 of pregnancy. This is generally long before the woman knows she is pregnant. It was also established that receiving enough folate from fortified foods was nearly impossible and supplements were highly recommended. Even though the studies successfully used the folate monoglutamate form of folic acid, it is the pteroylmonoglutamic acid form that is used in vitamin supplements and fortified foods. Most naturally occurring folates are pteroylpolyglutamates.

Folic acid deficiency is also common in tropical areas where poverty results in a poor diet. In North America and other regions of the world where access to food is rarely a problem, folic acid deficiency still occurs because dietary needs are not met, especially during the growth of children and adolescents and during pregnancy. These age groups are more prone to folic acid deficiency anemia because of their heavy use of folate-deficient cow's milk, which also inhibits the absorption of iron, causing an additional risk of iron-deficiency anemia as well.

Causes of folic acid deficiency anemia include:

- Impaired absorption because of intestinal dysfunction from such disorders as celiac disease, tropical sprue, regional jejunitis, Crohn's disease or bowel resection.
- Bacteria competing for available folic acid.

- Overcooking of food, destroying valuable water-soluble nutrients, including a high percentage of folic acid.
- Limited storage capacity in infants.
- Prolonged drug therapy, especially from anticonvulsants and estrogens.
- Not addressing increased folic acid needs of certain age groups, as well as in patients with neoplastic diseases and some skin disorders (e.g. chronic exfoliative dermatitis).
- Alcohol abuse (alcohol prevents absorption of several nutrients especially the B vitamins).
- Poor diets (common in alcoholics, the elderly, those living alone or in poverty and infants, especially those with infections or diarrhea).

CLINICAL FEATURES

Signs and symptoms of folic acid deficiency anemia gradually produces clinical features similar to other megaloblastic anemias, but without neurologic manifestations of B12 deficiency. Symptoms include the following:

- Gastrointestinal dysfunction
- Angular cheilitis
- Ulcerative stomatitis
- Pharyngitis
- Sore tongue
- Diarrhea
- Progressive fatigue
- Shortness of breath
- Heart palpitations
- Weakness
- Glossitis
- Nausea
- Anorexia
- Headache
- Fainting
- Irritability
- Forgetfulness
- Pallor
- Slight jaundice.

Blood Investigations

- Evaluation is based on blood tests and measurement of serum folate levels.
- Diagnosis is made following the Schilling test and a therapeutic trial of vitamin B12 injections to distinguish between folic acid deficiency anemia and pernicious anemia.
- Significant blood test findings include macrocytosis, decreased reticulocyte count, abnormal platelets and a serum folate less than 4 mg/ml.

Management

1. The oral administration of folic acid produces quick improvement in all symptoms; an adequate diet results in cure in cases due to simple malnutrition.
2. Conventional treatment consists primarily of folic acid supplements (about 400 mg three times daily) and, more importantly, the elimination of causes contributing to deficiency.
3. Oral administrations of folate preparations are 1 to 5 mg daily.
4. Prophylactic doses are given in pregnancy or those considering getting pregnant.
5. Parenteral administration of folic acid can relieve acute symptoms within 48 hours.
6. Blood transfusions are given to treat severe cardiac or respiratory distress as a result of severe deficiency.

PERNICIOUS ANEMIA AND VITAMIN B12 DEFICIENCY

It is a chronic hematologic disease with gastric atrophy and loss of intrinsic factor production in gastric secretions. Intrinsic factor is essential for absorption of vitamin B12 (erythrocyte-maturing principle). It is also called as vitamin B12 deficiency, Addisonian anemia, Hunter-Addison anemia, Lederer anemia, Biermer-Ehrlich anemia, Addison-Biermer disease. Pernicious anemia is a term reserved for patients with vitamin B12 deficiency due to a lack of production of intrinsic factor in the stomach.

ETIOPATHOGENESIS

- Gastric atrophy
- Autoimmune disorder with antiparietal cell antibodies associated with HLA types A2, A3 and B7 and A blood group.

CLINICAL FEATURES

- Usually rare before the age of 30 years, hence does not warrant a detailed description here
- Incidence in males > females
- Triad of symptoms—Weakness, sore painful tongue, numbness of extremities
- Fatigue, headache, nausea, vomiting, pallor, loss of weight and appetite
- Nervous system—Paresthesia of limbs, stiffness, irritability, depression, drowsiness. Degeneration of peripheral nerves and degeneration of myelin sheath.

Oral Manifestations

- Glossitis—Tongue is beefy red in color entirely or in patches. Small shallow ulcers.
- Glossodynia, glossopyrosis, gradual loss of papillae of tongue—Smooth or bald tongue called as Hunter's glossitis or Moeller's glossitis.

- Atrophy of taste buds on tongue is a common finding (Fig. 14.2)
- Nonspecific persistent stomatitis.
- Mucosa is intolerant to appliances.

Blood Investigations

- R.B.C count < 10,00,000 cells/cubic mm
- Macrocytosis (Fig. 14.3)
- Poikilocytosis
- Hemoglobin content is increased
- Advanced cases—Polychromatophilic cells, stippled cells, Howell-Jolly bodies and Cabot's rings-punctate basophilia
- WBCs are decreased in number but increased in size—Macropolycytes
- Mild to moderate thrombocytopenia
- Coexistent iron deficiency.

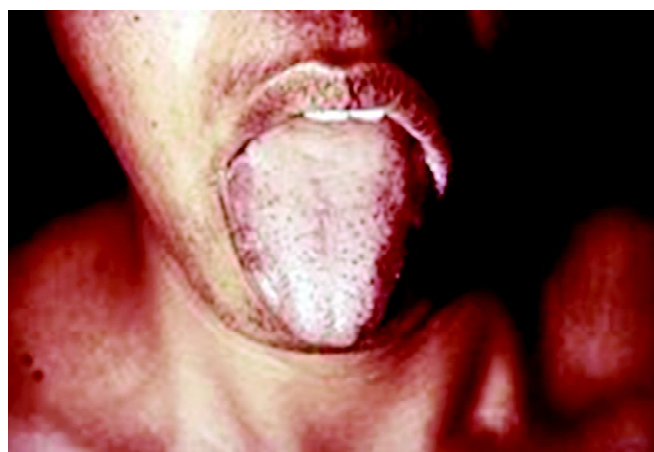


FIGURE 14.2: Pernicious anemia showing atrophy of taste buds on tongue

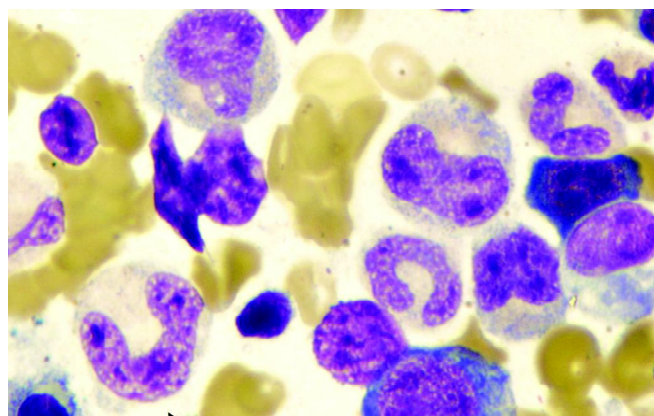


FIGURE 14.3: Pernicious anemia showing macrocytosis

Serum Investigations

- Indirect bilirubin elevated
- Serum lactate dehydrogenase increased.

Gastric Secretions

- Achlorhydria
- Intrinsic factor decreased or absent.

Bone Marrow

- Hypercellularity
- Trilineage differentiation
- Erythroid precursors are large and oval, nucleus is large and contains coarse motley chromatin clumps providing a “checker board appearance”
- Presence of giant platelets in smear.

Management

1. Administration of vitamin B12 and folic acid.
2. The mental and neurological damage can become irreversible without therapy.

APLASTIC ANEMIA

Aplastic anemia is a bone marrow failure syndrome characterized by peripheral pancytopenia and generalized lack of marrow activity.

Types

- Primary aplastic anemia
- Secondary aplastic anemia.

ETIOLOGY

- Primary aplastic anemia:
 - Unknown etiology
 - Fanconi’s Syndrome: Congenital aplastic anemia + bone abnormalities + microcephaly + hypogenitalism + olive brown pigmentation of skin.
- Secondary aplastic anemia:
 - Known etiology with a better prognosis
 - Exposure to various drugs, chemical substances, radiant energy. Chemicals may be amidopyrine, chloramphenicol, colloidal Ag, Hg, etc.

CLINICAL FEATURES

- Severe weakness, dyspnea, pallor of skin
- Numbness and tingling of extremities
- Petechiae in skin and mucous membrane due to platelet deficiency (Fig. 14.4)
- Increased infection due to neutropenia.



FIGURE 14.4: Purpuric rash on forearm seen in aplastic anemia

Oral Manifestations

- Petechiae and purpuric spots on oral mucosa
- Spontaneous gingival hemorrhage
- Ulcerative lesions of oral mucosa and pharynx may result in gangrene (lack of inflammatory response).

Laboratory Investigations

- Pancytopenia
- RBC count <10,00,000 cells/cu mm
- Decreased hematocrit and Hb levels
- Prolonged bleeding time
- Hypoplasia of bone marrow
- Severe cases—Fatty replacement of marrow and increased plasma cells and mast cells (Fig. 14.5).

Management

1. Blood transfusion.
2. Bone marrow transplantation.
3. Immunosuppressive therapy.
4. Consult patient’s physician before planning dental treatment.
5. Toothbrushing is contraindicated by most physicians. A soft toothbrush and gentle strokes may be permitted.
6. Mouthwashes are found to be ineffective.
7. Gentle rubbing with wet gauze is recommended.
8. Local anesthesia may be dangerous if platelet count is below 50,000/cu mm.
9. Prosthetic and orthodontic appliances are contraindicated.
10. Treatment contraindicated during an aplastic crisis.

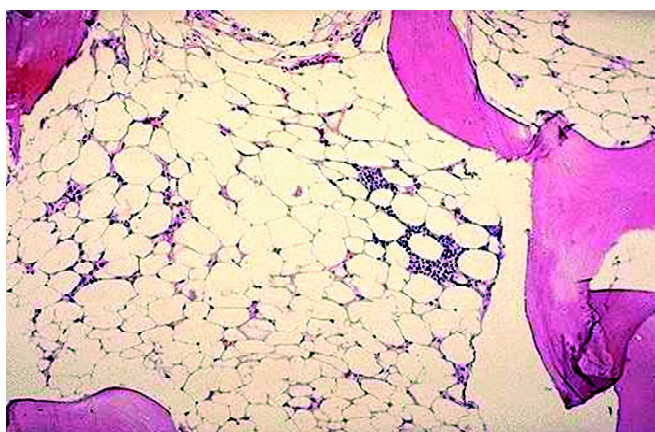


FIGURE 14.5: Aplastic anemia showing presence of more number of fat cells as compared to red cells

11. Aplastic crisis usually self-limiting with recovery in 7 to 10 days.
12. For ulcerations:
 - Soft bland diet
 - Topical anesthetics
 - Mouthrinses of 50:50 mixture of diphenhydramine and kaolin/pectin or dyclonine.

SICKLE CELL ANEMIA

Sickle-cell disease or sickle-cell anemia (or drepanocytosis) is a life-long blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications.

Linus Pauling and colleagues were the first, in 1949, to demonstrate that sickle-cell disease occurs as a result of an abnormality in the hemoglobin molecule.² This was the first time a genetic disease was linked to a mutation of a specific protein, a milestone in the history of molecular biology and it was published in their paper "sickle cell anemia, a molecular disease".

ETIOPATHOGENESIS

One-third of all indigenous inhabitants of sub-Saharan Africa carry the gene, because in areas where malaria is common, there is a survival value in carrying only a single sickle-cell gene (sickle cell trait). Those with only one of the two alleles of sickle-cell disease are more resistant to malaria, since the infestation of the malaria plasmodium is halted by the sickling of cells which it infests. Sickle-cell gene mutation probably arose spontaneously in different geographic areas, as suggested by restriction endonuclease analysis.

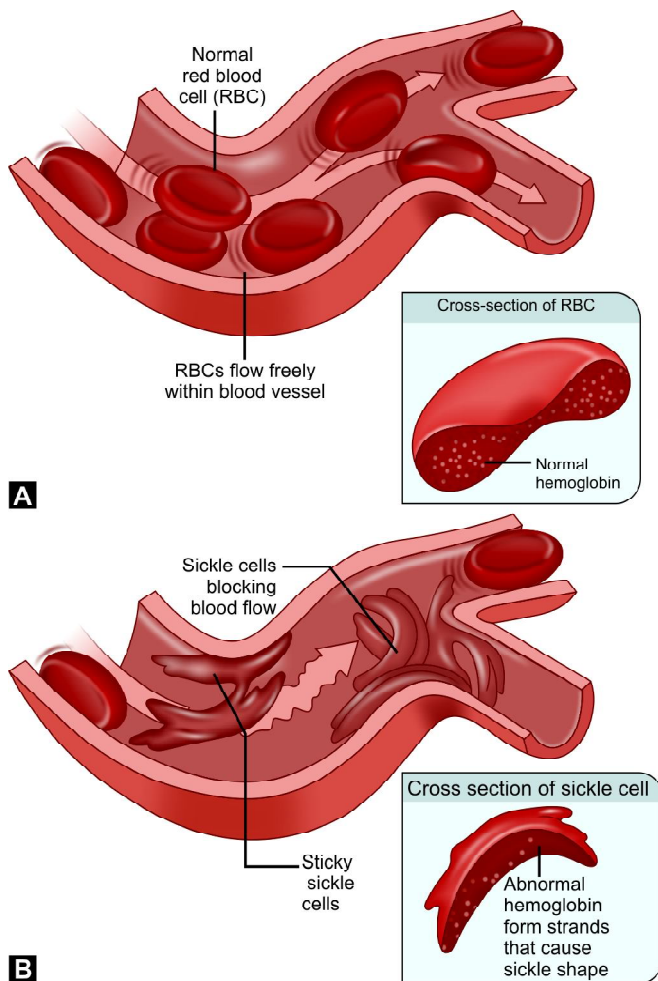
Sickling of erythrocytes occurs because of a point mutation in the β -globin chain of hemoglobin, causing the hydrophilic

amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position. The β -globin gene is found on the short arm of chromosome 11. The association of two wild-type β -globin subunits with two mutant β -globin subunits forms hemoglobin S (HbS). Under low-oxygen conditions (being at high altitude, for example), the absence of a polar amino acid at position six of the β -globin chain promotes the non-covalent polymerization (aggregation) of hemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity. Instead of being flexible and disc-shaped, these cells are more stiff and curved in the shape of the old farm tool known as a sickle—that is where the disease gets its name. The shape is similar to a crescent moon. This single amino acid change causes hemoglobin proteins to form fibers. In people heterozygous for HgbS (carriers of sickling hemoglobin), the polymerization problems are minor, because the normal allele is able to produce over 50 percent of the hemoglobin. In people homozygous for HgbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth donut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated. Under normal circumstances, these painful crises occur 0.8 times per year per patient.

The loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decreases the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia (Figs 14.6A and B).

The actual anemia of the illness is caused by hemolysis, the destruction of the red cells inside the spleen, because of their misshape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction. Healthy red blood cells typically live 90 to 120 days, but sickle cells only survive 10 to 20 days.

The allele responsible for sickle-cell anemia is autosomal incomplete dominant and can be found on the short arm of chromosome 11. A person that receives the defective gene from both father and mother develops the disease; a person that receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier. If two parents who are carriers have a child, there is a 1-in-4 chance of their child's developing the disease and a 1-in-2 chance of their child's being a carrier. Since the gene is incompletely recessive,



FIGURES 14.6A and B: Sickle cell anemia. (A) Showing normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin. (B) Showing abnormal, sickled red blood cells clumping and blocking blood flow in a blood vessel. (Other cells also may play a role in this clumping process.) The inset image shows a cross-section of a sickle cell with abnormal hemoglobin

carriers can produce a few sickled red blood cells, not enough to cause symptoms, but enough to give resistance to malaria. Because of this, heterozygotes have a higher fitness than either of the homozygotes. This is known as heterozygote advantage.

Due to the adaptive advantage of the heterozygote, the disease is still prevalent, especially among people with recent ancestry in malaria-stricken areas, such as Africa, the Mediterranean, India and the Middle East.³

Sickle-cell disease is inherited in the autosomal recessive pattern (Fig. 14.7).

1. If one parent has sickle-cell anemia (SS) and the other has sickle-cell trait (AS), there is a 50 percent chance of a

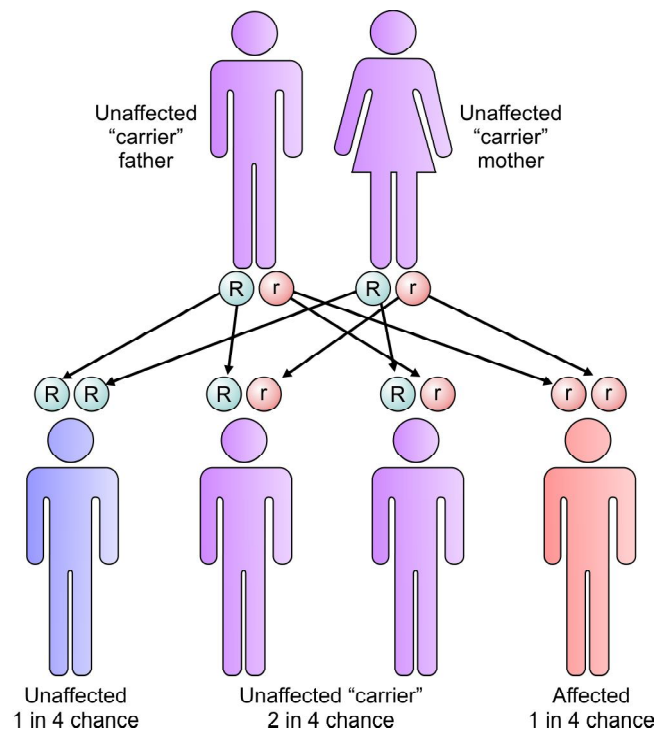


FIGURE 14.7: Diagrammatic representation of inheritance of sickle cell anemia

child's having sickle-cell disease (SS) and a 50 percent chance of a child's having sickle-cell trait (AS).

2. When both parents have sickle-cell trait (AS), a child has a 25 percent chance (1 of 4) of sickle-cell disease (SS), as shown in the diagram.

CLINICAL FEATURES

- Sickle-cell disease usually presents in childhood and occurs more commonly in people (or their descendants) from parts of tropical and sub-tropical regions where malaria is or was common. The prevalence of the disease in the United States is approximately 1 in 5,000, mostly affecting Americans of sub-Saharan African descent, according to the National Institute of Health.⁴ In the United States, about 1 in 500 black births have sickle-cell anemia.
- Life expectancy is shortened, with studies reporting an average life expectancy of 42 and 48 years for males and females, respectively.⁵
- *Uwakwe et al, 2002*, found that caffeine could hasten sickling as well as fragility of HbS erythrocytes in a concentration dependent manner.⁶
- No active hemolytic disease is generally seen before the age of two years.
- Medullary hypertrophy is seen in an attempt to replace the lysed erythrocytes.

Oral Manifestations

- **Robinson and Sarnat, 1952**, stated that 79.2 percent patients show jaw abnormalities.⁷
- **Mourshed and Tuckson, 1974**, found radiographic changes in the mandible in 85 percent of patients.⁸
- **Sanger and Bystrom, 1977**, noted a loss of alveolar bone in intra-oral periapical radiographs of all children examined.⁹
- A coarse trabecular “stepladder” pattern was seen in the jaw.
- Hypomineralization of dentin is seen.
- Interglobular dentin in the periapical area is evident with inclusions in the peripulpal dentinal tubules.
- Abrupt alteration of dentinogenesis with denticle like calcified bodies in the pulp chamber may be seen.
- Proliferation of cementum in the apical and midroot areas may be evident.

Laboratory Investigations

- In HbSS, the full blood count reveals hemoglobin levels in the range of 6 to 8 g/dL with a high reticulocyte count. In other forms of sickle-cell disease, Hb levels tend to be higher.
- A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).
- Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite (Fig. 14.8).
- The presence of sickle hemoglobin can also be demonstrated with the “sickle solubility test”. A mixture of hemoglobin S (HbS) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

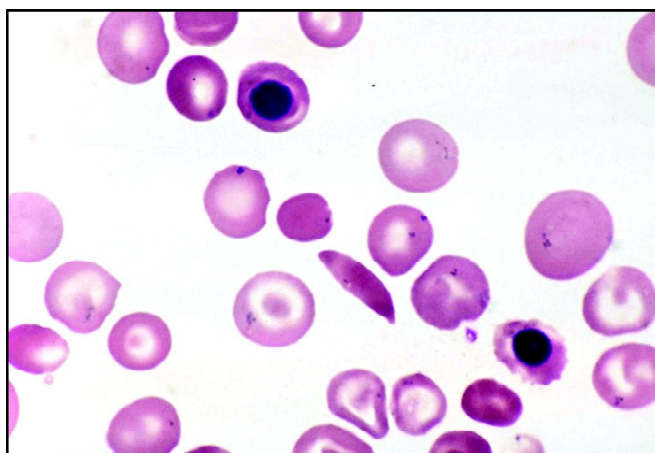


FIGURE 14.8: Peripheral smear showing sickle-shaped red blood cell

- Abnormal hemoglobin forms can be detected on hemoglobin electrophoresis, a form of gel electrophoresis on which the various types of hemoglobin move at varying speeds. The diagnosis can be confirmed with high-performance liquid chromatography (HPLC).
- Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.
- An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be routinely performed.

Bone Marrow

Bone marrow is hyperplastic (Fig. 14.9)

Management

1. Most people with sickle-cell disease have intensely painful episodes called vaso-occlusive crises. Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that is frequently prescribed by doctors in order to help control any itching associated with the use of opioids.
2. Children born with sickle-cell disease will undergo close observation by the pediatrician and will require management by a hematologist to assure they remain healthy. These patients will take a 1 mg dose of folic acid daily for life. From birth to five years of age, they will also have to take penicillin daily due to the

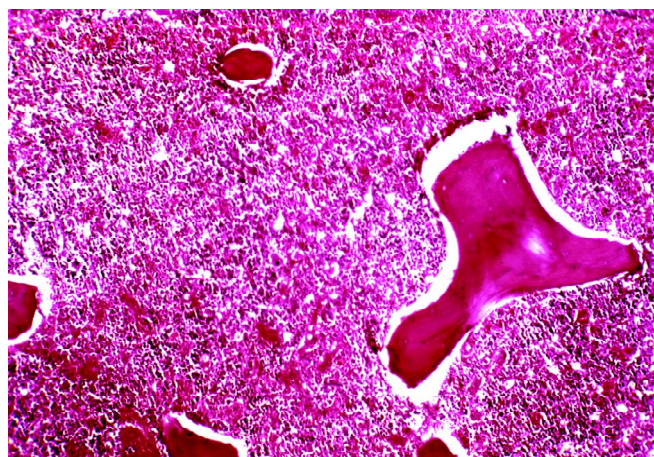


FIGURE 14.9: Sickle cell anemia showing hyperplastic marrow

immature immune system that makes them more prone to early childhood illnesses.

3. Acute chest crisis is managed in a manner similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since wall-deficient [atypical] bacteria are thought to contribute to the syndrome), oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patient's red cell mass for normal red cells, which decreases the percent of hemoglobin S in the patient's blood.
4. The first approved drug for the causative treatment of sickle-cell anemia, hydroxyurea, was shown by Charache et al, 1995, to decrease the number and severity of attacks¹⁰ and shown to possibly increase survival time in a study in 2003 by Steinberg et al.¹¹ This is achieved, in part, by reactivating fetal hemoglobin production in place of the hemoglobin S that causes sickle-cell anemia. Hydroxyurea had previously been used as a chemotherapy agent and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.
5. Bone marrow transplants have proven to be effective in children.
6. Fluid balance, body temperature regulation, patient positioning are extremely important.
7. Dietary cyanate, from foods containing cyanide derivatives, has been used as a treatment for sickle cell anemia. In the laboratory, cyanate and thiocyanate irreversibly inhibit sickling of red blood cells drawn from sickle cell anemia patients. However, the cyanate would have to be administered to the patient for a lifetime, as each new red blood cell created must be prevented from sickling at the time of creation. Cyanate also would be expelled via the urea of a patient in every cycle of treatment.
8. Treatment during a sickle cell crisis is contraindicated.
9. Sedative drugs to be used should not affect the respiratory rate.
10. Local anesthetics with vasoconstrictors are not contraindicated.
11. According to Stewart, N₂O – O₂ is not contraindicated if oxygen levels are closely monitored and 100 percent O₂ administered immediately on discontinuation of N₂O – O₂ sedation.
12. Pre-operative blood transfusion is recommended if Hb < 5 g/dL.
13. Presence of enamel hypomineralization dictates the institution of preventive measures to avoid caries or wearing away of tooth structure.

14. Prevention along with regular recalls is recommended for periodontal disease.
15. During general anesthesia, strict adherence to general principles, will avoid the onset of a sickle cell crisis.
16. Future treatments:
 - Various approaches are being sought for preventing sickling episodes as well as for the complications of sickle-cell disease. Other ways to modify hemoglobin switching are being investigated, including the use of phytochemicals such as nicosan. Gene therapy is under investigation. Another treatment being investigated is Senicapoc.¹²
 - People who are known carriers of the disease often undergo genetic counseling before they have a child. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used.

THALASSEMIA

Thalassemia is an autosomal recessive disorder that can affect the structure and synthesis of hemoglobin.

ETIOPATHOGENESIS

Beta thalassemia major results in a failure to produce β globin chains, impeding the synthesis of normal globin chains, leading to damage of the red cell membrane, followed by cell lysis and severe anemia. The body responds by increasing the production of erythrocytes, causing increased marrow capacity in bones and extra-medullary hematopoiesis, particularly in the spleen and liver.

CLINICAL FEATURES

- Clinical manifestations are seen within the first year of life.
- Failure to thrive, splenomegaly, poor appetite are commonly seen.
- Varying degrees of anemia and jaundice (Fig. 14.10) may be present.
- Recurrent ulcers on lower extremities may be seen.
- Protrusion of the middle-third of face due to enlargement of maxilla ("chipmunk facies") (Fig. 14.11), tightness of the upper lip are evident. This leads to an increased overjet and spacing of the upper incisors. The maxillary alveolar bone and the palate show a retruded position.
- Mandible becomes less enlarged compared to the maxilla, possibly because the dense cortical plates of the mandible prevent the expansion.

- Ocular hypertelorism, epicanthal folds, bronzing of the skin may be seen. Frontal bossing is evident (Fig. 14.12).
- Pain and swelling of the parotid glands and atrophic candidiasis have also been reported in these patients.
- Medullary hyperplasia, generalized osteoporosis show a “hair on end” appearance on a lateral skull radiograph (Fig. 14.13).
- Lamina dura may be thinned out with shortening of roots of the teeth.

RADIOGRAPHIC FEATURES

- Maxillary sinuses may be obliterated due to erythroid hyperplasia.
- There is generalized rarefaction of alveolar bone, thinning of cortical bone, coarse trabeculae of the jaws and a “chicken-wire” appearance of enlarged marrow spaces.

BLOOD INVESTIGATION

Thalassemia major shows small, pale (hypochromic), abnormally-shaped red blood cells (Fig. 14.14). Thalassemia minor shows small (microcytic), pale (hypochromic), variously-shaped (poikilocytosis) red blood cells (Fig. 14.15)

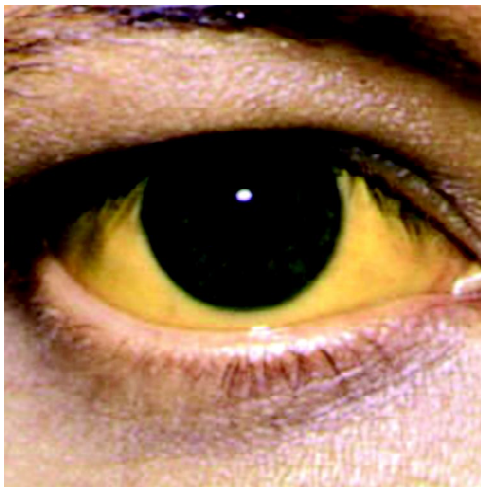


FIGURE 14.10: Thalassemia major showing yellowish discoloration of sclera



FIGURE 14.12: Thalassemia major showing frontal bossing in a child



FIGURE 14.11: Thalassemia major showing 'chipmunk facies'



FIGURE 14.13: Thalassemia major showing widening of the diploic space of the skull with thinning of the inner and outer tables produces a “hair on end” appearance

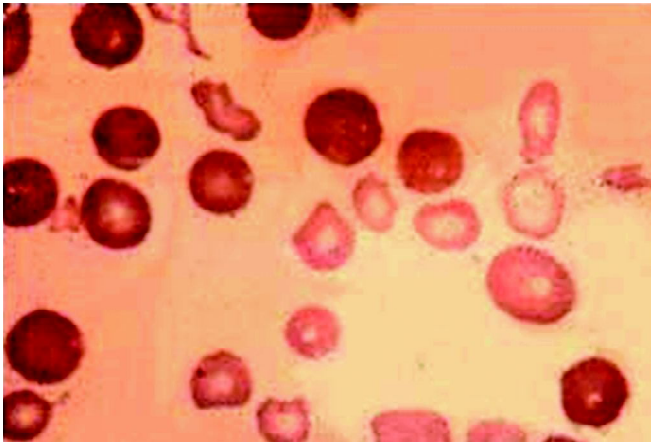


FIGURE 14.14: Thalassemia major showing small, pale (hypochromic), abnormally-shaped red blood cells

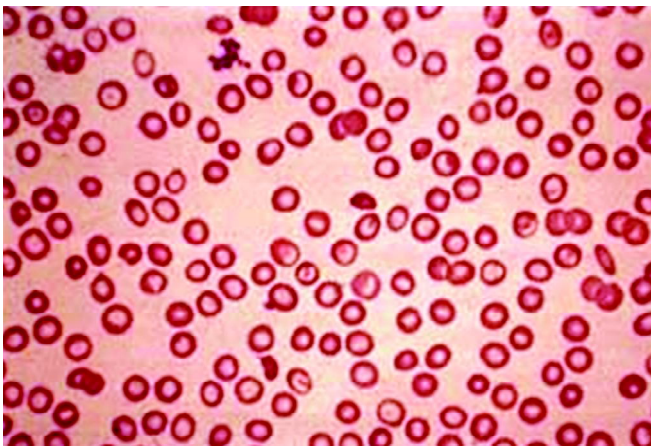


FIGURE 14.15: Thalassemia minor showing small (microcytic), pale (hypochromic), variously-shaped (poikilocytosis) red blood cells. These small red blood cells (RBCs) are able to carry less oxygen than normal RBCs

Management

1. Prevention of dental disease is paramount, hence the emphasis on pre- and post-natal counseling with anticipatory guidance and close follow-up.
2. In order to manage the organomegaly and skeletal changes, children start regular monthly blood transfusions from an early age (6–9 months), which continue through life if a hematopoietic cell transplant is not available.
3. Iron overload, the main cause of morbidity and mortality, is controlled by the iron-chelating drug desferrioxamine.
4. Conventional treatment related complications include post transfusional viral infections and multiple endocrine dysfunction, progressive liver fibrosis and cardiac disease due to iron overload.

5. Surgical correction of bony abnormalities of the maxilla may be done, but a relapse can be expected due to continued marrow expansion.
6. Dental treatment under local anesthesia and nitrous oxide-oxygen inhalation may be carried out normally, but decision on use of general anesthesia warrants a detailed preoperative consultation with an experienced anesthesiologist and the patient's physician due to cardiomyopathy, liver concerns and endocrine complications.
7. Allogenic stem cell transplantation is recommended and preferably should be done at an early age before the child has developed disease and complications associated with the therapies.

HEMOPHILIA

Hemophilia is a rare inherited disorder in which the blood does not clot normally. The word hemophilia is derived from Greek *haima* = blood, *philia* = friend.

CLASSIFICATION

Hemophilia may be of three types:

1. Hemophilia A—Also called as classic hemophilia—deficiency of factor VIII or antihemophilic factor.
2. Hemophilia B—Also called as Christmas disease—deficiency of factor IX or plasma thromboplastin component.
3. Hemophilia C—Deficiency of factor XI or plasma thromboplastin antecedent.
 - Incidence of Factor VIII deficiency—80 percent of patients suffering from hemophilia
 - Incidence of Factor IX deficiency—15 percent of patients suffering from hemophilia.

Hemophilia A and hemophilia B are classified into three groups based on the level of procoagulant present:

- Mild—Factor levels are 5 to 35 percent
- Moderate—Factor levels are 2 to 5 percent
- Severe—Factor levels are 0 to 1 percent.

Hemophilia C can be distinguished from hemophilia A (deficiency of factor VIII) and hemophilia B (deficiency of factor IX) by the absence of bleeding into joints and muscles and by its occurrence in individuals of either sex.

Unlike the bleeding tendency in hemophilia A or B, which is clearly related to the factor level, the bleeding risk in hemophilia C is not always influenced by the severity of the deficiency, especially in individuals with partial deficiency. This unpredictability makes hemophilia C more difficult to manage than hemophilia A or B.

VON WILLEBRAND'S DISEASE

It is a hereditary bleeding disorder resulting from an abnormality of von Willebrand factor (VWF) that is found in

plasma, platelets, megakaryocytes and endothelial cells. It circulates with factor VIII and is important in platelet adhesion to the subendothelium via collagen and is therefore important in formation of primary platelet plug. There is a qualitative and quantitative defect in the VWF. VWF is composed of subunits called as multimers. von Willebrand's disease is divided into subtypes based on platelet and plasma multicentric structure of the VWF. Impaired formation of the platelet plug may result in bleeding from the skin and mucosa, bruising, epistaxis, prolonged bleeding after surgical procedures and menorrhagia. This is in contrast to factors VIII and IX deficient hemophilia in which bleeding tends to involve muscles and joints.

ETIOLOGY

Transmission (Figs 14.16 and 14.17)

- Factor VIII and IX deficiency—X-linked recessive
- Factor XI deficiency—Autosomal recessive
- Von Willebrand disease—Autosomal dominant.

Hemophilia almost always affects boys because the disease is an X-linked genetic disorder, passed from mother to son. Boys get an X chromosome from their mother and a Y chromosome from their father. If the mother carries the gene for hemophilia on one of her X chromosomes, each of her sons will have a 50 percent chance of having hemophilia.

A mother who is a carrier also has a 50 percent chance of giving the faulty X chromosome to her daughter. That does not give the daughter the hemophilia disease, but it does result

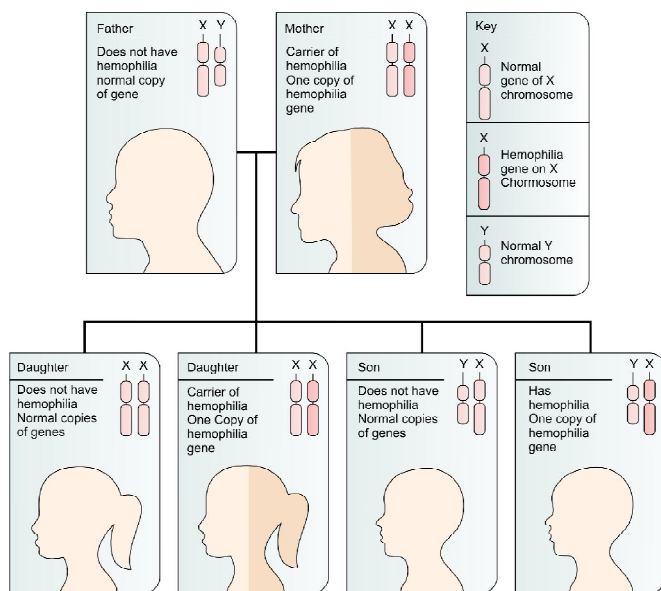


FIGURE 14.16: Schematic representation of inheritance pattern of hemophilia (normal father and carrier mother)

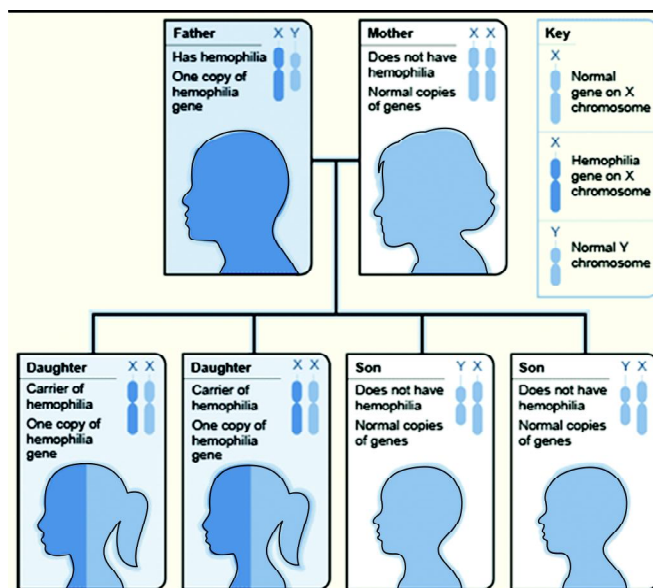


FIGURE 14.17: Schematic representation of inheritance pattern of hemophilia (hemophilic father and normal mother)

in the daughter becoming a hemophilia carrier. So it's possible one of her sons could have the disease.

CLINICAL FEATURES

- Usually no spontaneous hemorrhage during the first year of life.
- Ambulation often brings evidence of bruising.
- People who have hemophilia may bleed for a long time after an injury or accident.
- They also may bleed into their knees, ankles and elbows (hemarthroses) (Fig. 14.18). Bleeding in the joints causes pain and, if not treated, can lead to arthritis.
- Muscle atrophy, osteoporosis may be present.
- Spontaneous bleeding in severe cases is seen.
- **Mulkey, 1976**¹³ and **Stoneman and Deierl, 1975**,¹⁴ described hemophilic pseudotumors of the jaws.
- Intraosseous and subperiosteal hemorrhage is generally seen.
- Tooth displacement may be present.
- Mucous membrane hemorrhage may be present.
- Petechiae, ecchymoses are very common.
- Bleeding in the brain, a very serious complication of hemophilia requires emergency treatment.
- Babies who are learning to crawl usually bump into things, but ordinarily this doesn't cause swelling in their joints. If they do, it is a tip-off that there may be bleeding in the joints, which usually does not happen from normal activities or minor bumps.
- Excessive bleeding during menstruation may occur.



FIGURE 14.18: Hemarthrosis seen in hemophilia

- Psychosocial problems due to inability to play and mix with other children of the same age group and frequent visits to the hospital.

RADIOGRAPHIC FEATURES

- Enlargement of bony structures
- Delicate trabeculae
- Areas of radiolucency.

Management

1. Main principles of management are:
 - Prevention of dental disease.
 - Prevention of hemorrhage while the disease is being eliminated.
2. Brushing with a soft toothbrush and careful flossing.
3. Fluorides for prevention of dental caries.
4. Careful prophylaxis may not require replacement therapy.
5. Deep scaling may require transfusion of factor VIII concentrate or factor IX concentrate (monoclonal and recombinant).
6. Ultrasonic instruments are advocated for professional oral hygiene procedures.
7. Gingival packing may expose deep calculus to easier removal and avoid replacement therapy.
8. Infiltration local anesthesia is possible without factor coverage.
9. Intrapulpal injections are possible without factor coverage.
10. Aspiration of blood or hematoma formation following injection requires factor coverage and local control with ice packs.
11. Block anesthesia requires 30 to 50 percent factor levels.
12. **Mulkey, 1976**, advocated peridental injection to avoid requirement of replacement therapy.¹³

13. Slow atraumatic injections reduce post-operative complications.
14. Rubber dam clamps should be atraumatic to gingival tissues.
15. **Evans, 1977**, recommends a thin rubber dam to minimize clamp torque.
16. Saliva ejection is avoided to minimize suction hematoma.¹⁵
17. Wedges and matrices are crucial to retract papillae from the operative site.
18. Retraction cord during crown preparation is helpful in exposing marginal areas.
19. **Powell, 1974**, recommended that during pulp therapy, filling and filling should be 1 to 2 mm short of the radiographic apex.¹⁶
20. Most oral surgeries can be accomplished at a 30 to 50 percent replacement level.
21. Just before surgery, start with 7 to 10 day regimen of EACA (epsilon-amino caproic acid)—Loading dose 100-200 mg/kg followed by 100 mg/kg for 7 to 10 days.
22. Clear liquids for the first day after surgery.
23. Utensils, straws and hard foods should not be inserted in the mouth.
24. Milk and dairy products may aggravate clot dissolution.
25. Tissue borne primary tooth can be extracted using topically applied thrombin or other hemostatic agent and local pressure.
26. Cellulose bandage may be applied to protect the wound.
27. For a primary tooth with good bone support, extraction considerations should be same as that for a permanent tooth.
28. Placement of oxidized cellulose dipped in powdered or liquid thrombin in the apical portion of sockets helps control the hemorrhage.
29. Topical application of concentrated antihemophilic factor and microfibrillar collagen hemostat to sockets also helps in controlling hemorrhage after extraction.
30. Sutures may be used when appropriate.
31. For mild factor VIII deficient hemophilia, DDAVP (1-deamino-8-D-arginine vasopressin) may be used for minor hemorrhagic episodes to achieve hemostasis. DDAVP is a synthetic analog of vasopressin. This drug when given intravenously, subcutaneously or intranasally causes a rise in the factor VIII activity and the VWF often to the hemostatic range. Peak levels are obtained approximately one hour post administration. Repeated use of DDAVP may result in tachyphylaxis. DDAVP used to treat hemorrhagic disorders may also be associated with water retention, hyponatremia and rarely seizures. DDAVP may also be used to achieve hemostasis in type I von Willebrand's disease. Type I von Willebrand's disease is a quantitative deficiency of the von Willebrand factor with all multimers present.

32. Orthodontic therapy usually does not present a problem.
33. Drugs like aspirin, meperidine, phenacetin, oxycodone, ibuprofen, naproxen sodium are contraindicated.
34. Acetaminophen, propoxyphene, pentazocine may be prescribed for pain.
35. Patients with joint replacement may require antibiotic prophylaxis.
36. Patient with an inhibitor presents a tremendous challenge. Inhibitors are antibodies that may develop in approximately 28 percent of patients with severe factor VIII deficiency and in 35 percent of patients with severe factor IX deficiency. Patients with low responding inhibitors may continue to be treated with factor concentrate, whereas those with high responding inhibitors require the use of bypassing products (either PCC or activated PCC). Hemophiliacs with inhibitors pose a challenging treatment problem and should be managed in conjunction with a regional hemophilia comprehensive center, since hemostasis may be difficult to achieve.
37. Scientists are working on developing a gene therapy for people with hemophilia. Hemophilia is considered a good test for gene therapy because it is caused by only one defective gene. This could be a way to change the way someone's body works so that the body can produce the missing clotting factors on its own.

POLYCYTHEMIA

Polycythemia vera, also known as “erythremia”, is a blood disorder in which the bone marrow makes too many red blood cells. Polycythemia vera may also result in the overproduction of white blood cells and platelets. Most of the health concerns associated with polycythemia vera are caused by a blood-thickening effect that results from an overproduction of red blood cells.

TYPES

Relative polycythemia (pseudoerythrocytosis) is secondary to fluid loss or decreased fluid intake resulting in hemoconcentration. Two basic categories of polycythemia are recognized:

- Primary polycythemias due to factors intrinsic to red cell precursors, including primary familial and congenital polycythemia (PFCP), idiopathic erythrocytosis and polycythemia vera.
- Secondary polycythemias are caused by factors extrinsic to red cell precursors and include a physiologic-appropriate erythropoietin (Epo) production in response to tissue hypoxia and physiologic-inappropriate erythropoietin production not in response to tissue hypoxia.

ETIOPATHOGENESIS

In normal hematopoiesis, myeloid stem cells give rise to erythrocytes, platelets, granulocytes, eosinophils, basophils and monocytes. The production of each lineage is a function of cell proliferation, differentiation and apoptosis. These various stages of differentiation rely on multiple interrelated processes. Protein growth factors, known as cytokines, stimulate proliferation of the multilineage cells (e.g. interleukin [IL]-3, granulocyte-macrophage colony-stimulating activity [GM-CSF]). Other factors primarily stimulate the growth of committed progenitors (e.g. GM-CSF, macrophage colony-stimulating factor [M-CSF], erythropoietin [Epo]).

Erythropoiesis (Fig. 14.19) is a carefully ordered sequence of events.

Initially occurring in fetal hepatocytes, the process is taken over by bone marrow in the child and adult. Although multiple cytokines and growth factors are dedicated to the proliferation of the RBC, the primary regulator is Epo. Red cell development is initially regulated by stem cell factor (SCF), which commits hematopoietic stem cells to develop into erythroid progenitors. Subsequently, Epo continues to stimulate the development and terminal differentiation of these progenitors. In the fetus, Epo is produced by monocytes and macrophages found in the liver. After birth, Epo is produced in the kidneys; however, Epo messenger RNA (mRNA) and Epo protein are also found in the brain and in RBCs, suggesting that some paracrine and autocrine function is present as well.

Erythropoiesis escalates as increased expression of the *EPO* gene produces higher levels of circulating Epo. *EPO* gene expression is known to be affected by multiple factors, including hypoxemia, transition metals (Co^{2+} , Ni^{2+} , Mn^{2+}) and iron chelators. However, the major influence is hypoxia, including factors of decreased oxygen tension, RBC loss and increased oxygen affinity of hemoglobin. In fact, Epo

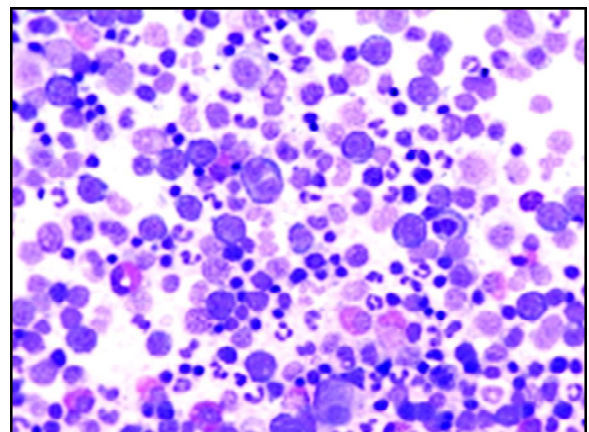


FIGURE 14.19: Bone marrow film demonstrating erythropoiesis

production has been observed to increase as much as 1000-fold in severe hypoxia.

Primary polycythemia is due to factors intrinsic to red cell precursors caused by acquired and inherited mutations. It includes the diagnoses of primary familial and congenital polycythemia, idiopathic erythrocytosis and polycythemia vera.

Currently, the diagnosis of polycythemia vera is based on the 2008 World Health Organization (WHO) criteria, which has integrated molecular diagnostics into the evaluation and screening for polycythemia vera.¹⁷ A diagnosis of polycythemia vera is made when both major and one minor criterion are present or when the first major criterion is present with any two minor criteria. The current criteria include the following:

Major Criteria

1. Hemoglobin level of more than 18.5 g/dL in men (> 16.5 g/dL in women) or other evidence of increased red cell volume.
Or
2. Hemoglobin or hematocrit level higher than 99th percentile of method-specific reference range for age, sex, altitude, of residence.
Or
3. Hemoglobin level of more than 17 g/dL in men (> 15 g/dL in women) if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that cannot be attributed to correction of iron deficiency.
Or
4. Elevated red cell mass greater than 25 percent above mean normal predicted value (Fig. 14.20).
Or
5. Presence of *JAK2*^{V617F} or similar mutation (e.g. *JAK2* exon 12 mutation).

Minor Criteria

1. Bone marrow trilineage myeloproliferation.
2. Subnormal serum Epo levels.
3. Endogenous erythroid colony growth (Fig. 14.21).

Until recently, the pathophysiology of polycythemia vera was unclear. In 2005, significant progress in the understanding of polycythemia vera was made with the discovery of a gain of function mutation in the tyrosine kinase *JAK2* (*JAK2*^{V617F}), which now appears to cause most primary cases in adults. *JAK2*^{V617F} is detectable in more than 95 percent of patients diagnosed with polycythemia vera. Several other mutations of *JAK2* have since been described (e.g. exon 12, *JAK2*^{H538-K539delinsI}). The *JAK2* mutations cause the enzyme to be constitutively active allowing cytokine independent proliferation of cell lines that express Epo receptors causing these cells to be hypersensitive to cytokines.¹⁸

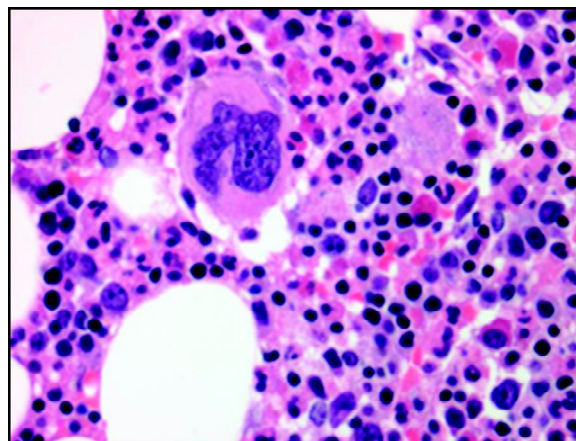


FIGURE 14.20: Polycythemia vera showing atypical large megakaryocytes with abnormal nuclear lobulation and eosinophilic nucleoli

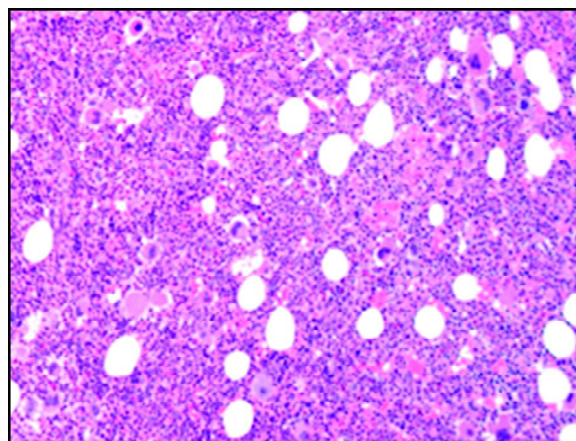


FIGURE 14.21: Bone marrow biopsy in polycythemia vera showing increased cellularity with predominantly erythroid hyperplasia

Familial clustering suggests a genetic predisposition. Whether these mutations are responsible for the development of polycythemia vera in pediatric patients is unclear. Some groups have reported lower rates of *JAK2* mutations in children compared with adults, whereas other groups have seen similar rates with complete or near complete presence of *JAK2*^{V617F} and other *JAK2* mutations. The prevalence of familial cases of chronic myeloproliferative disease is thought to be at least 7.6 percent, and the pattern of inheritance is consistent with an autosomal dominant pattern with decreased penetrance. Evidence of disease anticipation is noted in the second generation, presenting at a significantly younger age. However, clinical and hematological features in familial cases have not been shown to differ from those of sporadic mutations.

Secondary polycythemia may result from functional hypoxia induced by lung disease, heart disease, increased

altitude (hemoglobin increase of 4 percent for each 1000 m increase in altitude), congenital methemoglobinemia and other high-oxygen affinity hemoglobinopathies stimulating increased Epo production. Secondary polycythemia may also result from increased Epo production secondary to benign and malignant Epo-secreting lesions.

High altitude erythrocytosis is evident within the first week of high-altitude exposure. A sharp increase in Epo production is noticeable, with associated mobilization of iron stores with evidence of iron-deficient erythropoiesis. Abnormal high-affinity hemoglobin mutations characterized by left shift in the oxygen-hemoglobin dissociation curves lead to erythrocytosis.

Secondary polycythemia of the newborn is fairly common and is seen in 1 to 5 percent of all newborns in the United States. It results from either chronic or acute fetal hypoxia or delayed cord clamping and stripping of the umbilical cord. Aberrant erythropoietin production is seen with various renal, liver, CNS disorders and leads to physiologically inappropriate secondary polycythemia. Renal disorders frequently associated with polycythemia include renal cell carcinoma, Wilms tumor, polycystic kidneys, and renal transplantation. Erythrocytosis has also been documented in patients with hepatocellular carcinoma.

CLINICAL FEATURES

- Primary polycythemia is rare; the overall prevalence of polycythemia vera is 22 cases per 100,000 people.
- Only 0.1 percent of cases of polycythemia vera are observed in individuals younger than 20 years.
- The male-to-female ratio is 1.2 to 2.2:1 in adults and 1:1 in children.
- Symptoms of headache, vertigo, insomnia, weakness or malaise, pruritus (especially after exposure to warm water), bruising, ruddy or red appearance, erythromelalgia (burning pain, warmth and redness of extremities), diaphoresis/dyspnea, visual disturbance, ringing in the ears, paresthesias, arthropathies, weight loss, fullness of the abdomen, thirst, abdominal discomfort, constipation may be seen.
- Signs of rubor, especially facial rubor and sparing of the trunk, skin plethora, hypertension, both systolic and diastolic, hepatomegaly, splenomegaly (usually feels hard and smooth and occurs in more than two-thirds of patients), conjunctival plethora (engorged vessels in the bulbar conjunctiva), ecchymosis and cardiac hypertrophy (rarely observed) may be seen.
- The complications found in polycythemia vera are related to two primary factors. The first includes complications related to hyperviscosity. The second involves bone marrow-related complications. Untreated, the median survival time for these patients is 18 months. However, if patients are treated, survival is greatly extended, as many

as 10 to 15 years with phlebotomy alone. Blood count 6 to 7 million/cu mm.

- In the neonatal period, polycythemia-induced hyperviscosity can lead to altered blood flow and subsequently affect organ function. Infants with polycythemia are at increased risk for necrotizing enterocolitis, renal dysfunction, hypoglycemia and increased pulmonary vascular resistance with resultant hypoxia and cyanosis. Although initially thought to cause neurologic dysfunction, the decrease in cerebral blood flow seen in newborns with polycythemia is a physiologic response and does not appear to cause cerebral ischemia.

Management

1. Primary polycythemia: The goals of therapy are to maximize survival while minimizing the complications of therapy as well as of the disease itself.
 - Phlebotomy and myelosuppressive chemotherapy are the cornerstones of therapy and have produced a median survival time of 9 to 14 years after the beginning of treatment.
 - The goal of phlebotomy is to maintain normal red cell mass and blood volume, with a target hematocrit of less than 45 percent for men and less than 42 percent for women. The mean survival time of adult patients treated solely with phlebotomy is 13.9 years; however, a high risk of thromboembolic complications is observed.
 - In the past, the use of anticoagulants, including antiplatelet drugs such as aspirin and dipyridamole (Persantine), was associated with an increased risk of bleeding without an associated decrease in thrombotic events; therefore, anticoagulants have not previously been recommended. However, a large European study, results of which were published in the *New England Journal of Medicine* by Landolfi et al,¹⁹ showed a decrease in thrombotic events in those patients receiving low-dose aspirin therapy and recommended aspirin therapy for those patients for whom no contraindications were noted.
 - Hydroxyurea as a myelosuppressive agent is also widely used in high-risk patients with polycythemia vera (i.e. > 60 y, history of thrombosis) who require cytoreductive therapy, reducing the need for phlebotomy. However, similarly to those treated with chlorambucil, these patients also experience higher rates of malignancy.
 - Interferon alpha is effective in eliminating JAK2^{V617F} expression and inducing hematologic remission. Its use is limited by side effects, cost and route of administration. The pegylated form and low dose treatment has decreased the rate

of discontinuation of the drug secondary to side effects.

- In the past, patients have been treated with chlorambucil and busulfan. However, these patients exhibited the highest rates of secondary malignancy including acute leukemia, lymphocytic lymphomas and skin and GI carcinomas. The rates of malignancy appear lower with busulfan than with the other alkylating agents. Currently, these agents are rarely used.
 - Patients treated with phosphorus-32 (^{32}P) tolerate treatment well and have prolonged periods of remission. However, these patients also exhibit increased rates of acute leukemias (10-15%). The mean survival time with ^{32}P treatment is 10.9 years; therefore, phosphorous is rarely used.
 - Current recommendations for treatment of young patients primarily rely on phlebotomy because the thrombosis is far less likely to occur in children and the long-term risks of leukemia over a longer life span are increased.
2. Secondary polycythemia: Phlebotomy is used for symptomatic hyperviscosity. The goal is to treat the underlying cause of polycythemia.
 3. Surgery is not typically indicated. Occasionally, splenectomy is performed late in the course of the disease if massive splenomegaly causes adverse effects such as early satiety, anemia, or thrombocytopenia from sequestration.
 4. Please note that these patients have a high risk of complications during surgical procedures.
 5. Consult a neurologist and neurosurgeon if evidence of a stroke is present.
 6. Diet is unrestricted.
 7. Contact sports and other activities should be limited for individuals in hypercoagulable and hypocoagulable states.
 8. Current recommendations for treatment of young patients with polycythemia primarily rely on phlebotomy.
 9. Antineoplastic agents: The following medications are not approved for pediatric polycythemia but are extrapolated from other pediatric treatment regimens, including leukemia and myelodysplastic syndrome.
 - Interferon alfa 2a and 2b (Roferon-A [alfa-2a], Intron A [alfa-2b]): A recombinant purified protein used IV for CML, hairy cell leukemia and Kaposi sarcoma. Inhibits cellular growth and alters cell differentiation. Pediatric dose: 2.5 to 5 million U/d IM/SC.
 - Chlorambucil (Leukeran): Antineoplastic alkylating agent of nitrogen mustard type used for CLL, giant follicular lymphoma, Hodgkin lymphoma and lymphosarcoma. Pediatric dose is not established.

- Hydroxyurea (Hydrea): Inhibitor of deoxynucleotide synthesis. PO antineoplastic agent used in CML, melanoma, ovarian carcinoma and some head and neck carcinomas. Pediatric dose: 20 to 30 mg/kg/d PO (same as in adults).
- Busulfan (Myleran): Potent cytotoxic drug that, at recommended dosage, causes profound myelosuppression. As alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Pediatric dose: 0.06 to 0.12 mg/kg/d or 1.8 to 4.6 mg/m²/d PO; titrate dose to maintain WBC > 40,000/mL; reduce dose by 50 percent if WBC is 30,000 to 40,000/mL; discontinue if WBC < 20,000/mL.

LEUKOCYTOSIS

Leukocytosis is an abnormal increase in the number of circulating white blood cells. This condition may occur as a result of the reaction of the body to any pathologic situation.

It may be caused by an increase in (1) neutrophil count (i.e. neutrophilia), (2) lymphocyte count (i.e. lymphocytosis), (3) monocyte count (i.e. monocytosis), (4) eosinophilic granulocyte count (i.e. eosinophilia), (5) basophilic granulocyte count (i.e. basophilia), or (6) immature cells (e.g. blasts). A combination of any of the above may be involved.

NEUTROPHILIA (FIG. 14.22)

Neutrophils are phagocytic granulocytes that constitute an important component of the rapid “non-specific” immune defences. They, like other leucocytes, are derived from pluripotent stem cell progenitors in the bone marrow.

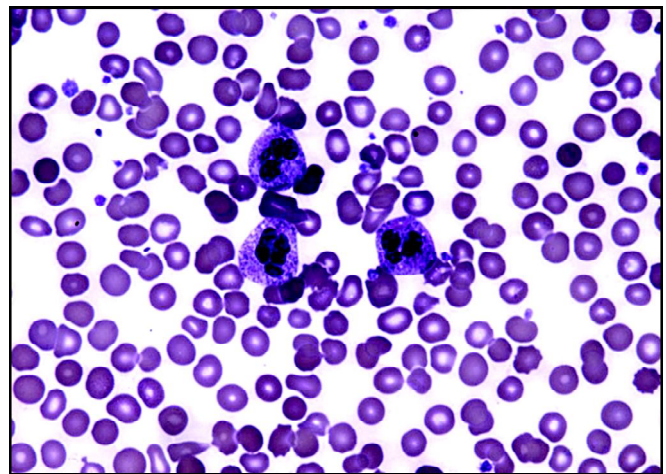


FIGURE 14.22: Increased number of neutrophils in neutrophilia

Upon stimulation by colony stimulating factors, including stem cell factor, granulocyte-monocyte colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF), phagocyte precursors proliferate and develop in the bone marrow to form mature segmented neutrophils. Increase in the number of circulating neutrophils is termed as neutrophilia.

Neutrophilia is divided into four categories based on the mechanism of neutrophilia: (1) increased production, (2) decreased egress from vascular space (demargination), (3) increased mobilization from the marrow storage pool and (4) reduced margination into the tissue.

ETIOLOGY

- Infection (bacterial, fungal)
- Trauma (surgery, burns)
- Malignancies (Hodgkin's lymphoma, juvenile myelomonocytic leukemia)

EOSINOPHILIA (FIG. 14.23)

An increase in absolute eosinophil count greater than $0.5 \times 10^9/L$ ($500/\mu L$) is generally considered eosinophilia. The following are common causes of eosinophilia:

- Allergy
- Hay fever, asthma, eczema
- Infection, Parasitic
- Skin disorders
- Connective tissue disorders
- Polyarteritis nodosa
- Malignancy solid tumor, lymphoma
- Myeloproliferative disease
- Chronic myeloid leukemia

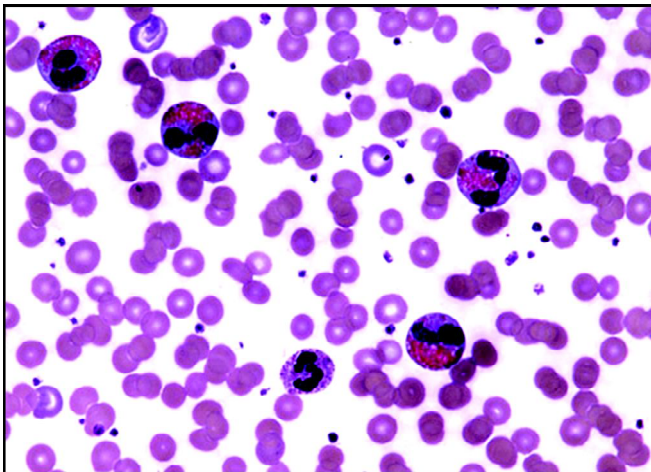


FIGURE 14.23: Increased number of granular eosinophils seen in eosinophilia

- Inflammation
- Acute hypersensitivity
- Ulcerative colitis
- Crohn's disease.

MONOCYTOSIS (FIG. 14.24)

Monocytosis is defined as a monocyte count that exceeds the upper limit of the reference range of $0.95 \times 10^9/L$ ($950/\mu L$).

Monocytosis is commonly caused by the following conditions:

1. Certain bacterial infections, e.g. tuberculosis, SABE, syphilis.
2. Viral infection.
3. Protozoal and rickettsial infections, e.g. malaria, typhus, kala-azar.
4. Convalescence from acute infection.
5. Hematopoietic disorders, e.g. monocytic leukemia, lymphomas, myeloproliferative disorders, multiple myeloma, lipid storage disease.
6. Malignancies, e.g. cancer of stomach, ovary, breast.
7. Granulomatous diseases, e.g. sarcoidosis, inflammatory bowel diseases.
8. Collagen vascular diseases.

BASOPHILIA

A basophil count that exceeds 0.10 to $0.15 \times 10^9/L$ (100 – $150/\mu L$) that leads to leukocytosis is rare.

AGRANULOCYTOSIS

Total lack of granulocytes in the blood is termed as agranulocytosis. These children suffer frequent infections from bacteria which in the past led to death in three-quarters of cases

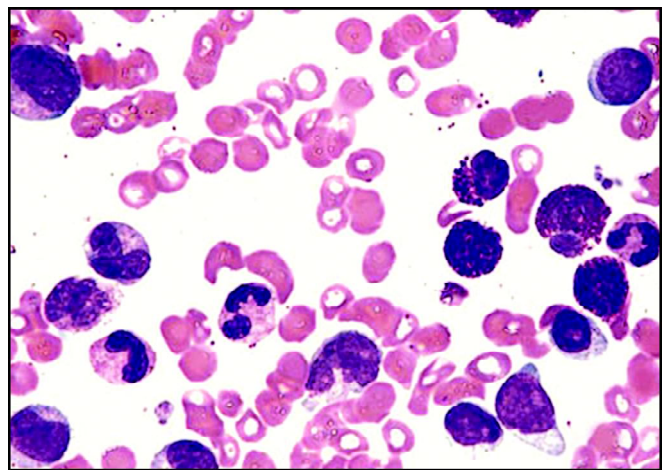


FIGURE 14.24: Increased number of monocytes seen in monocytosis

before three years of age. This disease is also known as severe congenital neutropenia (SCN). SCN was first clearly described by Kostmann in 1956.²⁰ It is now known to be caused by a defect in a gene on chromosome 1 (in *1p35-p34.3*) that codes for what is called the granulocyte colony-stimulating factor receptor (GCSFR). The inheritance of the disease is autosomal recessive.

Children with SCN have no special problems with viral or fungal infections. They do, however, have an increased risk of developing acute myelogenous leukemia or myelodysplasia, a bone marrow disorder. Aside from agranulocytosis, the bone marrow and blood show a number of other abnormalities (including maturational arrest of neutrophil precursors at the promyelocyte stage, absolute monocytosis, eosinophilia and thrombocytosis). The gamma globulin level in blood is low.

Other causes include cyclic neutropenia, irradiation by gamma rays, chemicals containing benzene or anthracene nuclei.

CLINICAL FEATURES

- Fever, chills, lymphadenopathy, weakness are common signs and symptoms.
- Oral mucosal ulcers and periodontal disease – most common,
- Ulcers resemble large deep scarring ulcers in major aphthous stomatitis
- Periodontal manifestations range from marginal gingivitis to rapidly advancing bone loss.

Management

1. Treatment with recombinant human granulocyte colony-stimulating factor (GCSF) elevates the granulocyte counts, helps resolve preexisting infections and diminishes the number of new infections and results in significant improvements in survival and quality of life. Some patients have developed leukemia or myelodysplastic syndrome following treatment with GCSF.
2. Congenital neutropenia is due to diverse causes. Not all patients with congenital neutropenia have mutations in the GCSFR gene.
3. Alternative names for severe congenital neutropenia (SCN) include: Kostmann's disease or syndrome, infantile genetic agranulocytosis and genetic infantile agranulocytosis.

NEUTROPENIA

Neutropenia is a rare disorder that causes children to have lower than normal levels of neutrophils, a type of white blood cell that destroys bacteria in the blood. Neutropenia can be a very serious condition because without enough neutrophils, a child is

susceptible to bacterial infections that can become life-threatening. The clinical symptoms of cyclic neutropenia are same as neutropenia only the disorder occurs in a cyclic manner. The cycles of decrease in neutrophil count occurs over a period of 21 days. The next few days, neutrophil count remains normal and then again the cycle of decrease in neutrophil count is repeated.

ETIOLOGY

Among children, neutropenia has a number of causes, including:

- Inadequate bone marrow production due to other blood disorders such as aplastic anemia or cancer such as leukemia.
- Response to radiation therapy or chemotherapy, which destroys white cells. When this occurs, it could delay radiation or chemotherapy.
- Inadequate white cells because of an autoimmune disease.
- Bacterial infections, such as tuberculosis, or viral infections like mononucleosis.

CLINICAL FEATURES

- Fever
- Shaking chills
- Sore throat
- Cough or shortness of breath
- Nasal congestion
- Diarrhea or loose bowels
- Burning during urination
- Unusual redness, swelling or warmth at the site of an injury
- Ulceration of oral mucosa – most common (Fig. 14.25).
- Lack surrounding inflammation and are characterized by necrosis
- Oral ulcers, advanced periodontal disease, pericoronitis and pulpal infection—potentially life threatening—can lead to bacteremia and septicemia

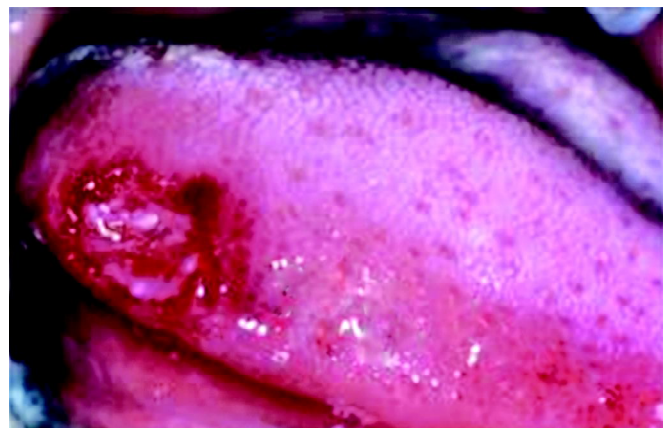


FIGURE 14.25: Ulcer on lateral border of tongue seen in neutropenia

- Peripheral blood smear reveals reduced number or absence of neutrophils (Fig. 14.26).

Management

- Treatment with granulocyte colony stimulating factors (G-CSFs) is the main option of treatment with severe congenital neutropenia.
- Corticosteroids may help if the neutropenia is caused by an autoimmune reaction. Removing an enlarged spleen may cure the neutropenia involved with hypersplenism.
- Bone marrow (or stem cell) transplantation may be recommended to treat certain serious causes of neutropenia, such as Kostmann syndrome, aplastic anemia or leukemia.

CLINICAL IMPORTANCE OF WBC COUNT

ANC	Significance
> 1500	Normal
500–1000	Patient at some risk for infection; defer elective procedures that could induce significant transient bacteremia
200–500	Patient must be admitted to hospital if febrile and given broad spectrum antibiotics; defer all elective dental procedures
< 200	At significant risk for sepsis

ANC = (% of neutrophils + % of bands) × total white count/100

LYMPHOCYTES

- Majority of lymphoid neoplasms are of B cell origin.
 - T cell tumor—CD2, CD3, CD4, CD7 and CD8 surface markers used.
 - B cell tumor—CD10, CD19, CD20 and surface markers are used.

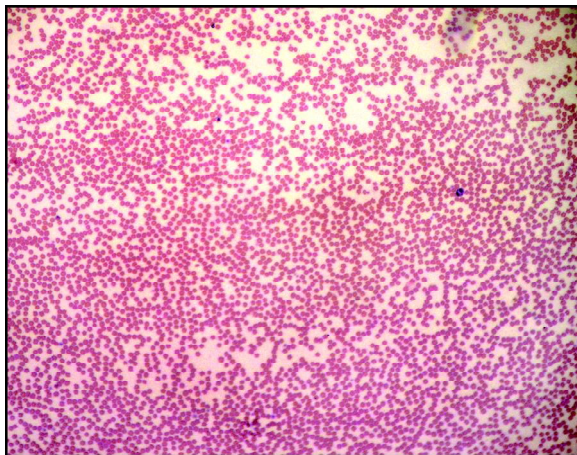


FIGURE 14.26: Absence of neutrophils seen in neutropenia

LYMPHOCYTOSIS

Lymphocytosis conventionally refers to a lymphocyte count greater than $4 \times 10^9/L$ ($4000/\mu L$); however, a lymphocyte count that exceeds this is physiologically present in infants and young children. The upper normal limit of lymphocyte count in this age group has not been well defined in a healthy population.

- Marked lymphocytosis is observed in individuals infected with pertussis.
- Viral infection generally causes lymphocytosis (relative or absolute) with or without neutropenia. Typical examples include infectious mononucleosis or cytomegalovirus infection, respiratory syncytial virus infections, and infectious hepatitis.
- Chronic lymphocytic leukemia is extremely rare in children and is usually not considered in the differential diagnosis of lymphocytosis.

LEUKEMIA

Leukemia is the progressive overproduction of white blood cells, which usually appear in the circulation in an immature form. The first published description of a case of leukemia in medical literature dates to 1827, when French physician Alfred-Armand-Louis-Marie Velpeau described a 63-year-old florist who developed an illness characterized by fever, weakness, urinary stones and substantial enlargement of the liver and spleen. Velpeau noted that the blood of this patient had a consistency “like gruel” and speculated that the appearance of the blood was due to white corpuscles.²¹ In 1845, a series of patients who died with enlarged spleens and changes in the “colors and consistencies of their blood” was reported by the Edinburgh-based pathologist JH Bennett; he used the term “leucocythemia” to describe this pathological condition.²²

The term “leukemia” was coined by Rudolf Virchow, the renowned German pathologist, in 1856. As a pioneer in the use of the light microscope in pathology, Virchow was the first to describe the abnormal excess of white blood cells in patients with the clinical syndrome described by Velpeau and Bennett. As Virchow was uncertain of the cause of the white blood cell excess, he used the purely descriptive term “leukemia” (Greek: “white blood”) to refer to the condition.²³ Wilhelm Ebstein introduced the term “acute leukemia” in 1889 to differentiate rapidly progressive and fatal leukemias from the more indolent chronic leukemias.²⁴ Finally, in 1900 the myeloblast, which is the malignant cell in AML, was characterized by Naegeli, who divided the leukemias into *myeloid* and *lymphocytic*.^{25,26}

TYPES OF LEUKEMIA

- Myeloid Leukemia—Involving granulocyte series
- Lymphoid Leukemia—Involving lymphocyte series
- Monocytic Leukemia—Involving monocyte series.

CLASSIFICATION

1. Acute myeloblastic leukemia (AML)
2. Acute lymphoblastic leukemia (ALL)
3. Chronic myeloid leukemia (CML)
4. Chronic lymphocytic leukemia (CLL).

ETIOLOGY

1. Genetic factors—Identical twins. Congenital disorders—Down's, Bloom's, Klinefelters's syndromes and Fanconi's anemia
2. Environmental factors
 - a. Ionizing radiation related to CML, AML and ALL but not CLL.
 - b. Chemical carcinogens—Benzene—AML.
 - c. Certain drugs—Alkylating agents—AML.
3. Infection—HTLV-I and HTLV-II.

PATHOGENESIS

- Malignant transformation of a single clone of cells of myeloid or lymphoid series, followed by proliferation of the transferred clone.
- In acute leukemia—Defect in maturation process of myeloid or lymphoid series.
- In leukemic transformation, the basic defect lies in DNA.
- Most consistent chromosomal abnormality is Philadelphia (Ph) chromosome.
- Leukemic cells accumulate in bone marrow and suppress normal hematopoietic stem cells.

ACUTE LEUKEMIAS

See Table 14.1.

ACUTE MYELOBLASTIC LEUKEMIA

Acute myeloid leukemia (AML), also known as acute myelogenous leukemia, is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, and its incidence increases with age. Hence this entity does not warrant a detailed discussion here.

CLINICAL FEATURES

1. Due to bone marrow failure:
 - a. Anemia producing pallor, lethargy, dyspnea.
 - b. Bleeding manifestations due to thrombocytopenia causing spontaneous bruises, petechiae, bleeding from gums.

TABLE 14.1: French-American-British classification²⁷

Lymphoblastic (ALL)

L1	Small monomorphic, high N:C ratio (Scores 0, 1, or 2)
L2	Large, heterogeneous, nucleolated, low N:C ratio (Scores-1, 2, or 3)
L3	Burkitt-cell type, basophilic, vacuolated

Myeloid (AML)

M0	Undifferentiated Myeloblastic (requires cell markers)
M1	Myeloblastic without maturation (requires cytochemistry: peroxidase or Sudan black B)
M2	Myeloblastic with maturation
M3	Hypergranular promyelocytic
M3-variant	Micro- or hypogranular bilobed promyelocytes
M4	Myelomonocytic with both granulocytic and monocytic differentiation
M5	Monoblastic (M5a requires cytochemistry: Alpha-naphthyl acetate esterase or Alpha-naphthyl butyrate esterase) and promonocytic-monocytic (M5b)
M6	Erythroleukemia, with > 50% erythroblasts and < 30% or > 30% blasts
M7	Megakaryoblastic (requires cell markers)

- c. Infection of mouth, throat, skin, respiratory, perianal sites.
 - d. Fever attributed to infections but sometimes idiopathic.
2. Due to organ infiltration:
 - a. Pain and tenderness of bones
 - b. Lymphadenopathy and enlargement of tonsils
 - c. Splenomegaly
 - d. Hepatomegaly
 - e. Leukemic infiltration of the kidney
 - f. Gum hypertrophy
 - g. Meningeal involvement
 - h. Chloroma or granulocytic sarcoma
 - i. CNS manifestations.

Acute myeloid leukemia (ALL), peripheral blood of a child, Pappenheim stain shows angel-wing—lobated nucleus and auer rods (Figs 14.27 and 14.28).

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is a form of leukemia, or cancer of the white blood cells characterized by excess lymphoblasts. Malignant, immature white blood cells continuously multiply and are overproduced in the bone marrow. ALL causes damage and death by crowding out normal cells in the bone marrow and by spreading (metastasizing) to other organs. It is the most common malignancy diagnosed in children, representing nearly one-third of all pediatric cancers.

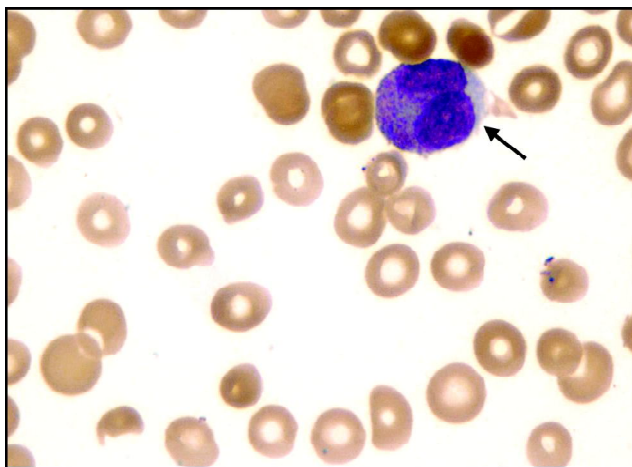


FIGURE 14.27: Acute myelogenous leukemia showing angel-wing-lobated nucleus (arrow)

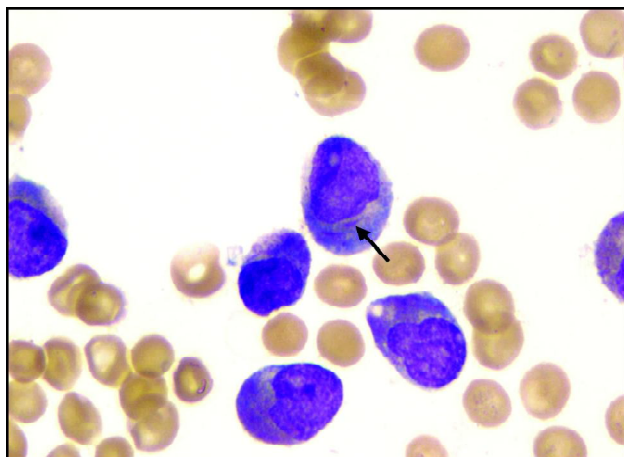


FIGURE 14.28: Acute myelogenous leukemia showing Auer rods (arrow)

ETIOPATHOGENESIS

Although a few cases are associated with inherited genetic syndromes (i.e. Down syndrome, Bloom syndrome, Fanconi anemia), the cause remains largely unknown. Many environmental factors (i.e. exposure to ionizing radiation and electromagnetic fields, parental use of alcohol and tobacco) have been investigated as potential risk factors, but none has been definitively shown to cause acute lymphoblastic leukemia. Various viruses may be linked to the development of leukemia, particularly when prenatal viral exposure occurs in mothers recently infected with influenza or varicella. However, no direct link has been established between viral exposure and the development of leukemia.

Acute lymphoblastic leukemia may also occur in children with various congenital immunodeficiencies (i.e. Wiskott-

Aldrich syndrome, congenital hypogammaglobulinemia, ataxia-telangiectasia) that have an increased predisposition to develop lymphoid malignancies.

In acute lymphoblastic leukemia, a lymphoid progenitor cell becomes genetically altered and subsequently undergoes dysregulated proliferation, survival and clonal expansion. In most cases, the pathophysiology of transformed lymphoid cells reflects the altered expression of genes whose products contribute to the normal development of B-cells and T-cells. Several studies indicate that leukemic stem cells are present in certain types of acute lymphoblastic leukemia. Another one-third of the ALL population exhibit one of four chromosomal translocations in the absence of increases in chromosomal number which can predict outcome. Three of the four translocations: t(1;19), mixed-lineage leukemia (MLL) translocations and the t(9;22) Philadelphia chromosome are associated with a poor prognosis while the most common translocation, t(12;21), predicts a favorable response.²⁸

CLASSIFICATION

WHO proposed classification of acute lymphoblastic leukemia.²⁸ The recent WHO International panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification mentioned below.

1. Acute lymphoblastic leukemia/lymphoma. Synonyms: Former FAB L1/L2
 - Precursor B acute lymphoblastic leukemia/lymphoma. Cytogenetic subtypes:
 - t(12;21)(p12,q22) TEL/AML-1
 - t(1;19)(q23;p13) PBX/E2A
 - t(9;22)(q34;q11) ABL/BCR
 - T(V,11)(V;q23) V/MLL.
 - Precursor T acute lymphoblastic leukemia/lymphoma.
2. Burkitt's leukemia/lymphoma. Synonyms: Former FAB L3.
3. Biphentotypic acute leukemia.

CLINICAL FEATURES

- The annual incidence rate for acute lymphoblastic leukemia is 30.9 cases per million populations.
- The peak incidence occurs in children aged two to five years.
- Acute lymphoblastic leukemia occurs slightly more frequently in boys than in girls. This difference is most pronounced for T-cell acute lymphoblastic leukemia.
- Children with acute lymphoblastic leukemia (ALL) generally present with signs and symptoms that reflect bone marrow infiltration and extramedullary disease. Because leukemic blasts replace the bone marrow, patients present with signs of bone marrow failure, including anemia,

thrombocytopenia and neutropenia. They also have signs of infection because of neutropenia.

- Clinical manifestations include fatigue and pallor, petechiae and bleeding and fever. In addition, leukemic spread may manifest as lymphadenopathy and hepatosplenomegaly.
- Other signs and symptoms of leukemia include weight loss, bone pain and dyspnea.
- Signs and symptoms of CNS involvement, even when it occurs, are rarely observed at the time of initial diagnosis. The signs and symptoms include headache, nausea and vomiting, lethargy, irritability, nuchal rigidity and papilledema.
- Cranial nerve involvement, which most frequently involves the seventh, third, fourth and sixth cranial nerves, may occur.
- Also, leukemia can present as an intracranial or spinal mass, which causes numerous neurologic symptoms, most of which are due to nerve compression.
- Testicular involvement at diagnosis is rare. However, if present, it appears as painless testicular enlargement and is most often unilateral.
- Careful neurologic examination to look for CNS involvement is important because the treatment for leukemia with CNS involvement is different.
- In male patients, testicular examination is necessary to look for testicular involvement of leukemia.
- Gingival bleeding.
- Gingival hypertrophy.
- Pain and numbness in the mandible.
- Candidiasis, ANUG, herpes simplex infections.
- Little effect of radiation treatment may be seen.
- Effects of long term chemotherapy on oral development are not well substantiated.
- Side effects of antineoplastic drugs may cause jaw pain and numbness.

Contrasting features between AML and ALL have been described in Table 14.2.

RADIOGRAPHIC FEATURES

- Loss of lamina dura
- Resorption of alveolar bone
- Alterations in the periodontal space
- Destruction of cancellous bone
- Alterations in crypts of developing teeth.

Acute lymphoblastic leukemia (ALL), peripheral blood of a child stained with Pappenheim stain shows round, slightly oval and indented nuclei with light staining and evenly dispersed nuclear chromatin (Fig. 14.29).

CHRONIC LEUKEMIAS

These are generally not seen in the pediatric age group, hence are out of the scope of this textbook (Table 14.2).

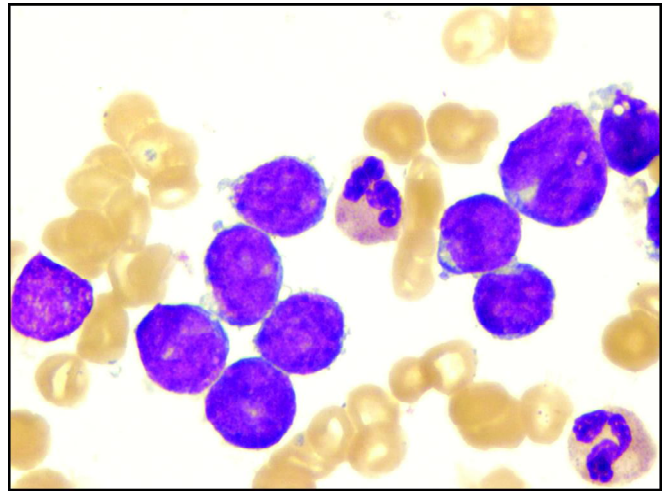


FIGURE 14.29: Acute lymphoblastic leukemia showing round, slightly oval and indented nuclei with light staining and evenly dispersed nuclear chromatin

Management

1. With improvements in diagnosis and treatment, overall cure rates for children with acute lymphoblastic leukemia now approach 80 percent. Further refinements in therapy, including the use of risk-adapted treatment protocols, may improve cure rates for patients at high risk while limiting the toxicity of therapy for patients with a low risk of relapse.
2. Because leukemia is a systemic disease, therapy is primarily based on chemotherapy. Different forms of acute lymphoblastic leukemia (ALL) require different approaches for optimal results. Excluding mature B-cell acute lymphoblastic leukemia which is treated with short-term intensive chemotherapy, including high-dose methotrexate (MTX), cytarabine and cyclophosphamide, acute lymphoblastic leukemia treatment typically consists of a remission-induction phase, intensification (consolidation) phase and continuation therapy targeted at eliminating residual disease. The addition of cyclophosphamide and intensive treatment with asparaginase is also beneficial in the treatment of T-cell acute lymphoblastic leukemia.
3. Tumor lysis syndrome
 - Before and during the initial induction phase of chemotherapy, patients may develop tumor lysis syndrome, which refers to the metabolic derangements caused by the systemic and rapid release of intracellular contents as chemotherapy destroys leukemic blasts.
 - Primary features of tumor lysis syndrome include hyperuricemia (due to metabolism of purines), hyperphosphatemia, hypocalcemia and hyperkalemia. The hyperuricemia can lead to crystal

TABLE 14.2: Contrasting features of AML and ALL

Sr. No.	Feature	AML	ALL
1.	Common age	Adults between 15–40 years; comprise 20% of childhood leukemias	Children under 15 years; comprise 80% of childhood leukemias
2.	Physical findings	Splenomegaly + Hepatomegaly + Lymphadenopathy + Bony tenderness + Gum hypertrophy +	Splenomegaly + Hepatomegaly + Lymphadenopathy + Bony tenderness + Meningeal involvement
3.	Laboratory findings	Low to high TLC; predominance of myeloblasts and promyelocytes in blood and bone marrow; thrombocytopenia moderate to severe	Low to high TLC; predominance of lymphoblasts in blood and bone marrow; thrombocytopenia moderate to severe
4.	Cytochemical stains	Cytosine arabinoside, anthracyclines (daunorubicin, adriamycin) and 6-thioguanine Myeloperoxidase, lysozyme, CD68	PAS +, acid phosphatase (focal) +
5.	Specific therapy	Cytosine arabinoside, anthracyclines and 6-thioguanine	Vincristine, prednisolone, anthracyclines and L-asparaginase
6.	Response to therapy	Remission rate low, duration of remission shorter	Remission rate high, duration of remission longer
7.	Median survival	12–18 months	Children without CNS prophylaxis 33 months, with CNS prophylaxis 60 months; adults 12–18 months

formation with tubular obstruction and possibly, acute renal failure requiring dialysis. Therefore, electrolyte and uric acid levels should be closely monitored throughout initial therapy.

- To prevent complications of tumor lysis syndrome, patients should initially receive intravenous (IV) fluids at twice the maintenance rates, usually without potassium.
 - Sodium bicarbonate is added to the IV fluid to achieve moderate alkalinization of the urine (pH level, 7.5–8) to enhance the excretion of phosphate and uric acid. A urine pH level higher than this should be avoided to prevent crystallization of hypoxanthine or calcium phosphate.
 - The standard treatment for malignancy-associated hyperuricemia also includes allopurinol. By blocking the enzyme xanthine oxidase, allopurinol blocks uric acid formation.
 - Rasburicase, a recombinant urate oxidase, has demonstrated increased efficacy in pediatric patients at high risk for tumor lysis by catalyzing the enzymatic oxidation of uric acid to a much more urine soluble product, allantoin.

4. Phases of therapy

- The treatment of childhood acute lymphoblastic leukemia, with the exception of B-cell acute

lymphoblastic leukemia, has 5 components: induction, consolidation, interim maintenance, delayed intensification and maintenance. The goal of induction is to achieve remission or less than 5 percent blasts in the bone marrow. Induction therapy generally consists of 3 to 4 drugs, which may include a glucocorticoid, vincristine, asparaginase and possibly an anthracycline. This type of therapy induces complete remission based on morphology in more than 98 percent of patients.

- Consolidation therapy is given soon after remission is achieved, to further reduce the leukemic cell burden before the emergence of drug resistance and relapse in sanctuary sites (i.e. testes, CNS). In this phase of therapy, the drugs are given at doses higher than those used during induction or the patient is given different drugs (i.e. high-dose MTX and 6-mercaptopurine [6-MP]), epipodophyllotoxins with cytarabine, or multiagent combination therapy.
- In interim maintenance, oral medications are administered to maintain remission and allow the bone marrow to recover. This occurs for 4 weeks and is followed by delayed intensification, which is aimed at treating any remaining resistant leukemia cells.
- The last phase of treatment is maintenance. This consists of intrathecal MTX every 3 months, monthly vincristine, daily 6-MP and weekly MTX.

5. Duration of therapy

- Whereas B-cell acute lymphoblastic leukemia is treated with a 2-month to 8-month course of intensive therapy, achieving acceptable cure rates for patients with B-precursor and T-cell acute lymphoblastic leukemia requires approximately 2 to 2.5 years of continuation therapy. Attempts to reduce this time, results in high relapse rates after therapy is stopped.
- Most contemporary protocols include a continuation phase based on weekly parenterally administered MTX given with daily, orally administered 6-MP interrupted by monthly pulses of vincristine and a glucocorticoid. Although these pulses improve outcomes, they are associated with avascular necrosis of the bone. Patients with high-risk acute lymphoblastic leukemia may also benefit from intensified continuation therapy that includes the rotational use of drug pairs.
- Improvements in relapse-free survival gained by intensification with anthracyclines or epipodophyllotoxins must be weighed against the late sequelae of these agents, which include cardiotoxicity and treatment-related acute myeloid leukemia.

6. Treatment of subclinical CNS leukemia is an essential component of acute lymphoblastic leukemia therapy. Although cranial irradiation effectively prevents overt CNS relapse, concern about subsequent neurotoxicity and brain tumors has led many investigators to replace irradiation with intensive intrathecal and systemic chemotherapy for most patients. This strategy has produced excellent survival outcomes, with CNS relapse rates of less than 2 percent in some studies.

7. High-risk patients: Optimal treatment for patients with very high-risk acute lymphoblastic leukemia has not been found. Some centers recommend allogeneic stem-cell transplantation (SCT) soon after first remission is achieved. For patients without a matched family donor, transplantation of marrow from an unrelated donor is a reasonable treatment option. Results of SCT, often reported from single institutions, have been inconsistent and sometimes disappointing. Large, multi-institutional, controlled trials are clearly needed to determine the effectiveness of this therapy for patients without a matched donor.

8. Molecular targeted therapy: A drug targeted at the underlying molecular defect that is unique to certain leukemias can have potent and specific antileukemic activity while producing minimal toxicity to normal cells. The best example of molecular targeted therapy is imatinib mesylate, a selective *BCR-ABL* tyrosine kinase inhibitor.

9. Numerous consultations should be obtained, depending on the clinical circumstances of patients with newly diagnosed acute lymphoblastic leukemia.

- Pediatric oncologist: Refer all patients to a subspecialist to direct their care.
- Pediatric surgeon: Patients require placement of a central venous catheter.
- Psychosocial team: Involve psychologists and social workers in the care of patients with acute lymphoblastic leukemia to aid them and their families in navigating all of the difficult issues surrounding their care.
- Radiation oncologist: Depending on their risk group, some patients require craniospinal radiation as part of the treatment plan.
- Other subspecialists: Consultations with other specialists (i.e. infectious disease specialist, nephrologist) may be appropriate, depending on the clinical circumstances.

10. Oral and dental considerations in leukemia:

- For patient whose 1st remission has not been obtained or is in relapse, all elective dental procedures should be deferred.
- However, potential source of infection to be removed, e.g. extraction of grossly carious tooth.
- Patient with remission but undergoing chemotherapy can undergo routine restorative and surgical procedures but blood profile to be taken before procedure.
- Patient with complete remission for two years is treated normally.
- Endodontic treatment not recommended in leukemic patients.
- Topical treatment to stop gingival bleeding includes removal of local irritants and direct pressure.
- Absorbable gelatin or collagen sponges, topical thrombin or placement of microfibrillar collagen can be helpful.

Oral rinses of antifibrinolytic agents such as tranexamic acid or α -aminocaproic acid to stop gingival bleeding have been reported.

- Platelet transfusion—Last resort to stop significant gingival hemorrhage.
- Treatment of caries and other dental infections should be definitive.
- Removal of local irritants and scrupulous oral hygiene for gingivitis.
- Supragingival scaling if patient in remission.
- Saline rinses if patient not in remission.
- Prophylactic antibiotic coverage.
- Bacterial infections—Penicillin.
- Fungal infections—Nystatin.
- Severe mycotic infections—Amphotericin B.
- Ulcers—Topical viscous lidocaine – 2 percent or dyclonine – 0.5 percent.
- Artificial saliva products (explained in the section on xerostomia).

Guidelines for Oral and Dental Management of Leukemia

1. Detection

- History
- Examination
- Screening laboratory tests:
 - White cell count
 - Differential white cell count
 - Smear for cell morphologic study
 - Hemoglobin or hematocrit level
 - Platelet count.

2. Referral

- Medical diagnosis
- Treatment.

3. Consultation before any dental care is rendered

- Current status
- Review of dental treatment needs
- Dental management plan.

4. Routine dental care

- None for patient with acute symptoms
- Once disease is under control, patient may receive indicated dental care
- Scaling and surgical procedures:
 - Bleeding time on day of procedure; if normal, proceed; if prolonged, delay or obtain platelet replacement

- Prophylactic antibiotic therapy to prevent post-operative infection (if severe neutropenia is present).

5. Emergency dental care

- Treatment of oral ulcers:
 - Antibiotics
 - Bland mouth rinse
 - Antihistamine solutions
 - Orabase.
- Oral candidiasis—Treat with antifungal medication.
- Conservative management of pain and infection
 - Antibiotic sensitivity testing
 - Antibiotics for infection
 - Strong analgesics for pain.

DISORDERS OF HEMOSTASIS

PLATELET DISORDERS

See Figure 14.30.

THROMBOCYTOPENIA

Thrombocytopenia is a condition in which the blood contains a reduced number of platelets, which are necessary for blood clotting. Thrombocytopenia, defined as a platelet count of less than 150,000/ L, is clinically suspected when there is a history of easy bruising or bleeding in a child. It may also present as an incidental finding during routine evaluation or during laboratory investigations performed for other reasons.

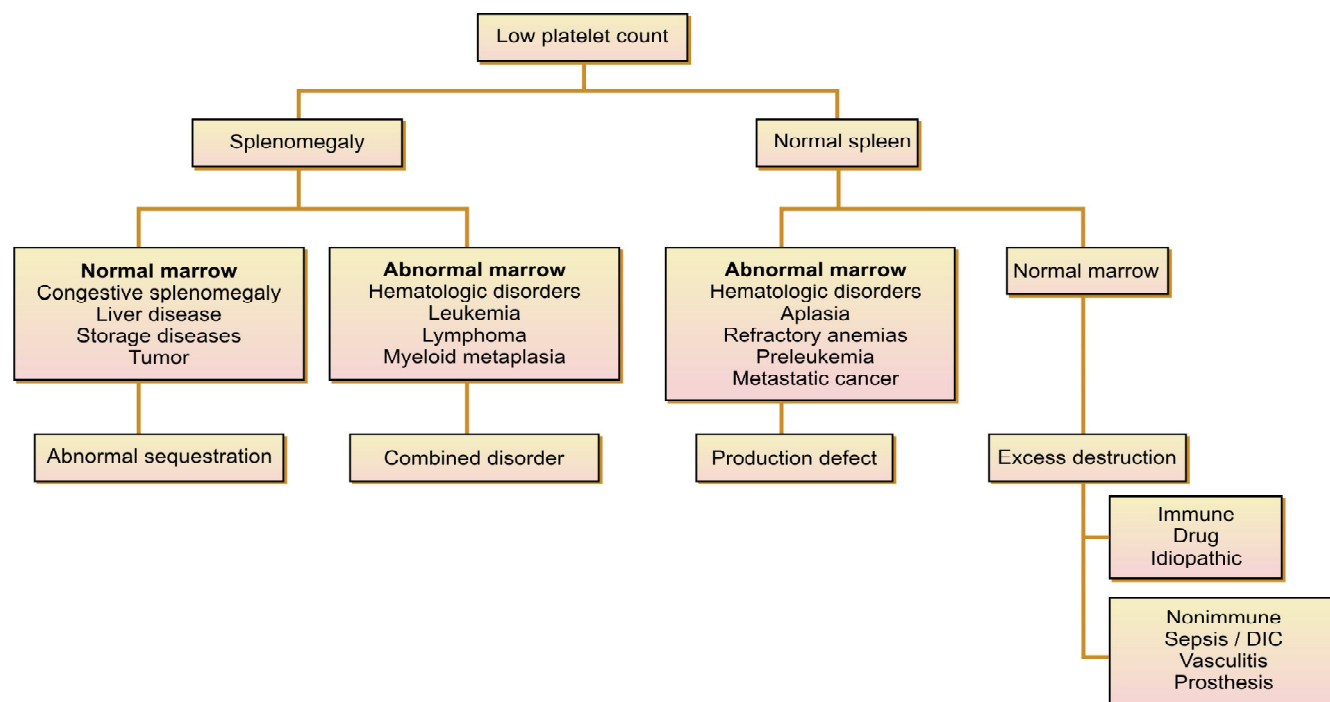


FIGURE 14.30: Schematic representation of classification of platelet disorders

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and the absence of other causes of thrombocytopenia. The two distinct clinical syndromes manifest as an acute condition in children and a chronic condition in adults.

ITP is a decrease in the number of circulating platelets in the absence of toxic exposure or a disease associated with a low platelet count.

PATHOPHYSIOLOGY

The normal platelet count for children ranges from 150,000 to 450,000/ L . In general, the risk of bleeding does not increase until the platelet count falls significantly below 1,00,000/ L . For example, surgical bleeding solely due to a decreased platelet count typically does not occur until the platelet count is less than 50,000/ L ; whereas, spontaneous bleeding does not occur until the platelet count is less than 20,000/ L .

ITP is primarily a disease of increased peripheral platelet destruction, with most patients having antibodies to specific platelet membrane glycoproteins. Relative marrow failure may contribute to this condition, since studies show that most patients have either normal or diminished platelet production.

Acute ITP often follows an acute infection and has a spontaneous resolution within two months. Chronic ITP persists longer than six months without a specific cause.

CLINICAL FEATURES

- Hemorrhage represents the most serious complication; intracranial hemorrhage is the most significant. The mortality rate from hemorrhage is approximately one percent in children and five percent in adults.
- Spontaneous remission occurs in more than 80 percent of cases in children but is uncommon in adults.
- In acute ITP (children), distribution is equal between males (52%) and females (48%).
- Peak prevalence occurs in children aged two to four years. Approximately 40 percent of all patients are younger than 10 years.
- History of bleeding, other illnesses, medications like heparin, quinidine/quinine, sulfonamides may be present.
- Common signs, symptoms and precipitating factors include the following:
 - Abrupt onset (childhood ITP)
 - Gradual onset (adult ITP)
 - Menorrhagia
 - Epistaxis
 - Recent live virus immunization (childhood ITP)
 - Recent viral illness (childhood ITP)

- Bruising tendency
- Nonpalpable petechiae, which mostly occur in dependent regions
- Hemorrhagic bullae on mucous membranes
- Purpura (Fig. 14.31)
- Gingival bleeding
- Signs of Gastrointestinal bleeding
- Menometrorrhagia, menorrhagia
- Retinal hemorrhages
- Evidence of intracranial hemorrhage, with possible neurologic symptoms
- The prevalence of palpable spleen in patients with ITP is approximately the same as that in the non-ITP population (i.e. 3% in adults, 12% in children)
- Spontaneous bleeding when platelet count is less than 20,000/ mm^3 .

Blood picture in thrombocytopenia shows low platelet count (Fig. 14.32). Thrombocytopenia may occur commonly in children as the bone marrow contains only one day storage of platelets.

Management

1. Life-threatening bleeding requires conventional critical care interventions.
2. In a patient with known ITP, high-dose parenteral glucocorticoids and IV immunoglobulin (IVIg), with or without platelet transfusions, are appropriate.
3. Platelet transfusion is indicated for controlling severe hemorrhage. Send a blood specimen to the lab for type and screen in case platelet transfusion is necessary.
4. Platelet survival is increased if the platelets are transfused immediately after IVIg infusion.
5. A consultation with a hematologist may be required to make a decision regarding the transfusion of platelets.



FIGURE 14.31: Thrombocytopenia showing purpuric rashes on whole body of an infant

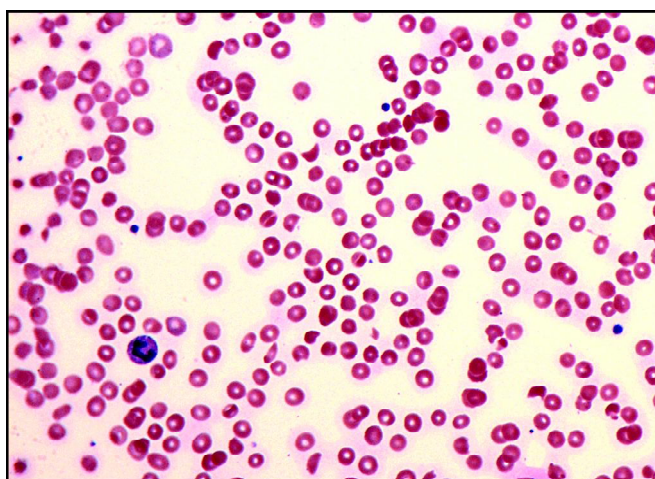


FIGURE 14.32: Thrombocytopenia showing low platelet count

6. Guidelines for transfusion dosage:
 - a. 6 to 8 U of platelet concentrate, or 1 U/10 kg.
 - b. 1 U of platelets to increase count of a 70-kg adult by 5-10,000/mm³ and an 18-kg child by 20,000/mm³.
7. Splenectomy is reserved for patients in whom medical therapy fails. Emergent splenectomy is indicated in patients with life-threatening bleeding in whom medical therapy fails.
8. Glucocorticoids and IVIg are the mainstays of medical therapy. Indications for use, dosage and route of administration are based on the patient's clinical condition, the absolute platelet count and the degree of symptoms. Consultation with a hematologist may be needed prior to starting therapy.
9. Children who have platelet counts > 30,000/mm³ and are asymptomatic or have only minor purpura do not require routine treatment. Children who have platelet counts < 20,000/mm³ and significant mucous membrane bleeding and those who have platelet counts < 10,000/mm³ and minor purpura should receive specific treatment.
10. Steroid use, usage of immunosuppressive drugs and splenectomy may be undesirable because of their associated complications.
11. According to one study, using a combination of weekly vincristine, weekly methylprednisolone, both until platelet counts reached 50,000/mm³ and cyclosporine orally twice daily until the platelet count is normal for 3 to 6 months seems promising.
12. Other therapies, such as cyclophosphamide, danazol, dapsone, interferon alfa, azathioprine, vinca alkaloids, accessory splenectomy and splenic radiation have been studied.
13. Clinical trials have shown promise for agents that directly stimulate platelet production, such as thrombopoietin (TPO) receptor-binding agents. While

they show promise for raising platelet counts, there are potential safety concerns such as thrombocytosis and rebound thrombocytopenia.

14. Dental considerations:

- a. Post extraction antifibrinolytic agents should be administered (e.g. to tranexamic acid, 25 mg/kg t.i.d.) for three to five days.
- b. Local measures to limit and control hemorrhage should be employed.
- c. Patient should be kept on a soft diet for seven days.

LYMPHOMA

Cancer can basically be divided into leukemia (mainly in blood and bone marrow) and solid tumors, where one or more lumps are the likely origin of disease. Lymphomas are solid tumors which can involve many different parts of the body and can present at different ages. Some lymphomas resemble leukemias in their pattern of spread and are treated with leukemia-type treatment protocols. Because the various types of lymphomas behave in different ways, it is best to consider them under individual groupings.

A number of different classification systems exist for lymphoma. In the mid 1990s, the Revised European-American Lymphoma (REAL) Classification attempted to apply immunophenotypic and genetic features in identifying distinct clinicopathologic NHL entities.²⁹

NEW WHO CLASSIFICATION OF LYMPHOID NEOPLASMS (2008)³⁰

Precursor Lymphoid Neoplasms

- B lymphoblastic leukemia/lymphoma NOS
- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukemia/lymphoma with t(9;22); bcr-abl1
- B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged
- B lymphoblastic leukemia/lymphoma with t(12;21); TEL-AML1 and ETV6-RUNX1
- B lymphoblastic leukemia/lymphoma with hyperploidy
- B lymphoblastic leukemia/lymphoma with hypodiploidy
- B lymphoblastic leukemia/lymphoma with t(5;14); IL3-IGH
- B lymphoblastic leukemia/lymphoma with t(1;19); E2A-PBX1 and TCF3-PBX1
- T lymphoblastic leukemia/lymphoma.

Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma

- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
- Heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extravascular plasmacytoma
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Primary cutaneous follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma, NOS
- (T-cell/histiocyte-rich type; primary CNS type; primary leg skin type and EBV+ elderly type)
- Diffuse large B-cell lymphoma with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma associated with HHV8+ Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, Burkitt-like
- B-cell lymphoma, unclassifiable, Hodgkin lymphoma-like.

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK-cells.
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoproliferative disorder of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell lymphoma/leukemia
- Extranodal T-cell/NK-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepato-splenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder
- Primary cutaneous gamma-delta T-cell lymphoma

- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK+ type
- Anaplastic large cell lymphoma, ALK- type.

Hodgkin Lymphoma (Hodgkin Disease)

Nodular lymphocyte-predominant Hodgkin lymphomas

- Classic Hodgkin lymphomas
- Nodular sclerosis Hodgkin lymphoma
- Lymphocyte-rich classic Hodgkin lymphoma
- Mixed cellularity Hodgkin lymphoma
- Lymphocyte depletion Hodgkin lymphoma.

Post-Transplant Lymphoproliferative Disorders (PTLD)

- Plasmacytic hyperplasia
- Infectious mononucleosis like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B and T/NK cell types)
- Classic HD type PTLD.

Histiocytic and Dendritic Cell Neoplasms

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Indeterminate dendritic cell sarcoma
- Disseminated juvenile xanthogranuloma.

HODGKIN'S DISEASE

Hodgkin's lymphoma causes the cells in the lymphatic system to abnormally reproduce, eventually making the body less able to fight infection and cause swelling in the lymph nodes. Thomas Hodgkin published the first description of lymphoma in 1832, specifically of the form named after him; Hodgkin's lymphoma.³¹ Hodgkin's lymphoma cells can also spread to other organs and tissue and cause metastasis.

ETIOLOGY

- The specific cause of Hodgkin's lymphoma is unknown.
- It is possible that a genetic predisposition and exposure to viral infections may increase the risk for developing Hodgkin's lymphoma.
- There is a slightly increased chance for Hodgkin's lymphoma to occur in siblings and cousins of patients.
- There has been much investigation into the association of the Epstein-Barr virus (EBV) which causes infection

mononucleosis; as well as of human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS). Both of these infectious viruses have been correlated with a greater incidence of children diagnosed with Hodgkin's lymphoma, although the direct link is unknown.

CLINICAL FEATURES

- Hodgkin's lymphoma accounts for about five percent of childhood cancers
- Hodgkin's lymphoma occurs most often in people between the ages of 15 and 34 and in people over age 55
- The disease, for unknown reasons, affects males more than twice as often as females
- Painless swelling of the lymph nodes in neck, underarm, groin and chest
- Difficulty in breathing (dyspnea) due to enlarged nodes in the chest
- Fever
- Night sweats
- Tiring easily (fatigue)
- Weight loss/decreased appetite
- Itching skin (pruritus)
- Frequent viral infections (i.e. cold, flu, sinus infection).

STAGING OF LYMPHOMA

The Ann Arbor classification is named after Ann Arbor, Michigan, where the Committee on Hodgkin's Disease Staging Classification met in 1971.³²

- Stage I—Usually involves a single lymph node region or structure.
- Stage II—Involves two or more lymph node regions or structures on the same side of the body.
- Stage III—Involves lymph node regions or structures on both sides of the body and is further classified depending on the organs and areas involved.
- Stage IV—Involves the disease in other areas (metastasis), in addition to the lymphatic system involvement.
- Stages are also noted by the presence or absence of symptoms of the disease:
 - Asymptomatic (A)
 - Symptomatic (B).

HISTOPATHOLOGIC FEATURES

- It is comprised of two main forms:
 1. Nodular lymphocyte predominant Hodgkin's lymphoma
 2. Classical Hodgkin's lymphoma
 - i. Lymphocyte rich
 - ii. Nodular sclerosis

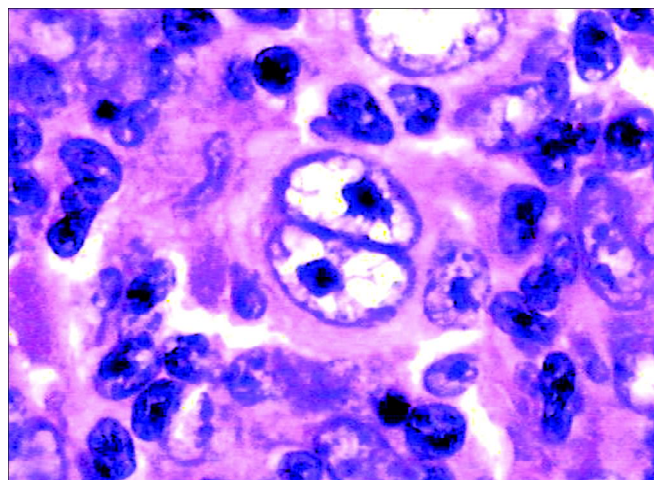


FIGURE 14.33: Hodgkin's lymphoma showing Reed-Sternberg cell

- iii. Mixed cellularity
- iv. Lymphocyte depletion
- v. Unclassifiable.
- Lesional area in case of lymphoma consists of inflammatory cell infiltrate interspersed with large, atypical neoplastic lymphoid cells. Classical Hodgkin's lymphoma consists of 'Reed-Sternberg' cells that are binucleated (resembling an 'owl-eye') or multinucleated atypical cells with prominent nucleoli³³ (Fig. 14.33)
- Nodular lymphocyte predominant Hodgkin's lymphoma shows 'popcorn cells' showing resemblance of nuclei to that of kernel of popped corn.
- Lymphocyte rich subtype of classical Hodgkin's lymphoma shows sheets of small lymphocytes with few 'Reed-Sternberg' cells.
- Nodular sclerosis subtype shows 'Reed-Sternberg' cells within the clear space and thus they are referred to as lacunar cells.
- Mixed cellularity subtype shows mixture of lymphocytes, plasma cells, eosinophils and histiocytes with abundant Reed-Sternberg cells (Fig. 14.34).
- Lymphocyte depletion subtype as the name suggests shows bizarre Reed-Sternberg cells with less or reduced number of lymphocytes.
- When lymphomas do not fit in any of the above subtypes, they are termed as unclassifiable.

DIAGNOSIS

Lymphoma is diagnosed by:

- Blood and urine tests
- X-rays of the chest
- Lymph node biopsy

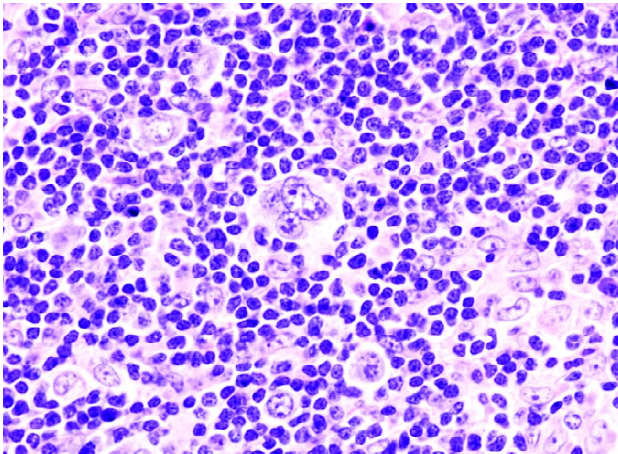


FIGURE 14.34: Hodgkin's lymphoma of mixed cellular variety

- Computed tomography scan of the abdomen, chest and pelvis
- Lymphangiogram (LAG)
- Bone marrow biopsy/aspiration.

Management

1. Chemotherapy is the mainstay of treatment which can often lead to remission.
2. Patients who have limited disease (stages 1 and 2) are managed by local radiation therapy alone.
3. Recent treatment trends however, combine less extensive radiotherapy fields with milder multiagent chemotherapy regimens.
4. Patients with stage 3 or 4 disease require chemotherapy; radiation therapy is used conjointly if significant mediastinal involvement or residual disease is detected.
5. Widely used regimen to treat Hodgkin's lymphoma is known as MOPP (Mechlorethamine, Oncovin, Procarbazine, Prednisone). Due to long term side effects of this regimen, another regimen known as ABVD (Adriamycin, Bleomycin, Vinblastine, DTIC) is often used.
6. Surgery.
7. Bone marrow transplant.
8. Supportive care (for pain, fever, infection and nausea or vomiting) is required.
9. Continued follow-up care (to determine response to treatment, detect recurrent disease and manage side effects of treatment) is essential.

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma is a cancer of the lymphatic system in which the cells in the lymphatic system reproduce abnormally, eventually causing tumors to grow. Non-Hodgkin's disease cells can also spread to other organs and tissues in the body.

ETIOLOGY

- The specific cause of non-Hodgkin's lymphoma is unclear. It is possible that genetics and exposure to viral infections may increase the risk for developing this malignancy.
- Non-Hodgkin's lymphoma has also been linked to chemotherapy and radiation therapy. Non-Hodgkin's may be a secondary malignancy as a result of treatment for certain cancers.
- There has been much investigation into the association of the Epstein-Barr virus (EBV) that causes the mononucleosis infection; as well as the human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS). Both of these infectious viruses have been linked to the development of Burkitt's lymphoma.
- The majority of Burkitt's lymphoma cases result from a chromosomal rearrangement between chromosome 8 and 14, which causes genes to change positions and function differently, promoting uncontrolled cell growth. Other chromosomal rearrangements have been seen in non-Hodgkin's lymphoma (all types) that are also thought to promote excessive cell growth.
- Children and adults with other hereditary abnormalities have an increased risk of developing non-Hodgkin lymphoma, including patients with ataxia telangiectasia, X-linked lymphoproliferative disease, or Wiskott-Aldrich syndrome.

The **Working Formulation** is a classification of non-Hodgkin lymphomas published in 1982.³⁴ It has since been replaced by other lymphoma classifications but is still used by cancer agencies for compilation of lymphoma statistics.

GRADES

Low grade

- Malignant Lymphoma, small lymphocytic (chronic lymphocytic leukemia)
- Malignant Lymphoma, follicular, predominantly small cleaved cell
- Malignant Lymphoma, follicular, mixed (small cleaved and large cell).

Intermediate grade

- Malignant Lymphoma, follicular, predominantly large cell
- Malignant Lymphoma, diffuse, small cleaved cell
- Malignant Lymphoma, diffuse, mixed small and large cell
- Malignant Lymphoma, diffuse, large cell.

High grade

- Malignant lymphoma, large cell, immunoblastic
- Malignant lymphoma, lymphoblastic
- Malignant lymphoma, small non-cleaved cells (Burkitt's lymphoma).

Miscellaneous

- Composite
- Mycosis fungoides
- Histiocytic
- Extramedullary plasmacytoma
- Unclassifiable.

CLINICAL FEATURES

- Lymphomas are the third most common childhood cancer. They occur most often in children between the ages of 7 and 11, but can occur at any age from infancy to adulthood.
- Non-Hodgkin's lymphoma affects males more often than females and is more common among Caucasian children than among African-American children and children of other races.
- Some children with non-Hodgkin's lymphoma have symptoms of an abdominal mass and have complaints of abdominal pain, fever, constipation and decreased appetite due to the pressure and obstruction a large tumor in this area can cause.
- Some children with non-Hodgkin lymphoma have symptoms of a mass in their chest and have complaints of respiratory problems, pain with deep breaths (dyspnea), cough and/or wheezing.
- Because of the rapid onset of this malignancy, any respiratory symptoms can quickly worsen, causing a life-threatening emergency.
- Other symptoms include:
 - Painless swelling of the lymph nodes in neck, chest, abdomen, underarm, or groin
 - Fever
 - Sore throat
 - Fullness in groin area from node involvement
 - Bone and joint pain
 - Night sweats
 - Tiring easily (fatigue)
 - Weight loss/decreased appetite
 - Itching of the skin
 - Recurring infections.

CLASSIFICATION

Staging and classification of non-Hodgkin's lymphoma is based on the extent of the disease and the specific cells involved.

Non-hodgkin's lymphoma in children is almost always one of three types:

- *Lymphoblastic non-Hodgkin's lymphoma:* Lymphoblastic non-Hodgkin's lymphoma accounts for about 30 percent of

the cases, involves the T-cells and usually presents with a mass in the chest, swollen lymph node(s), with or without bone marrow and central nervous system involvement.

- *Burkitt's or non-Burkitt's lymphoma:* Burkitt's or non-Burkitt's lymphoma is a non-Hodgkin's disease in which the cells are undifferentiated and diffuse. This has also been referred to as small non-cleaved cells. Burkitt's and non-Burkitt's lymphoma accounts for about 40 to 50 percent of the cases and is usually characterized by a large abdominal tumor and may have bone marrow and central nervous system involvement.
- *Large cell or diffuse histiocytic non-Hodgkin's lymphoma:* Large cell or diffuse histiocytic non-Hodgkin's lymphoma involves the B-cells and T-cells and accounts for about 25 percent of the cases. Children with this type of non-Hodgkin's lymphoma usually have lymphatic system involvement, as well as involvement of a non-lymph structure (i.e. lung, jaw, brain, skin and bone).
- *Large cell anaplastic lymphoma:* Large cell anaplastic lymphoma is a less common type of lymphoma in children. Treatment for this type is the same as for large cell lymphoma.

Staging of non-Hodgkin's Lymphoma³²

- Stage I—Involves the tumor at one site, either nodal or elsewhere in the body.
- Stage II—Involves the tumor at two or more sites on the same side of the body.
- Stage III—Involves tumors in any number that occur on both sides of the body, but does not involve bone marrow or the central nervous system.
- Stage IV—Any stage of tumor that also has bone marrow and/or central nervous system involvement. Stage IV is also subdivided depending on the amount of blasts (cancer cells) present in the bone marrow.

HISTOPATHOLOGIC FEATURES (Fig. 14.35)

- Non-Hodgkin's lymphomas are classified as low grade, intermediate grade and high grade histopathologically.
- Low grade lesions show well-differentiated small lymphocytes.
- High grade lesions show less differentiated cells.
- The histologic pattern may be nodular in which large clusters of cells are seen or diffuse in which cells are monotonous with no evidence of germinal center formation.
- Two cell types are seen in nodular type: Centrocytes that are small, irregular with cleaved nuclei and scant cytoplasm and centroblasts that are large cells with open nuclear chromatin, several nucleoli and moderate amount of cytoplasm. The cells in the diffuse form have open vesicular nuclei but sometimes cleaved nucleus may be present.

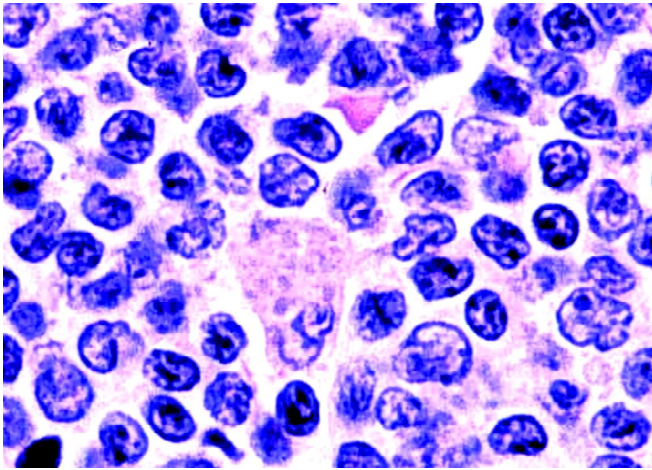


FIGURE 14.35: Non-Hodgkin's lymphoma showing scant cytoplasm and irregular shaped nuclei of lymphocytes

DIAGNOSIS

Diagnosis of non-Hodgkin's lymphoma is made by:

- Blood and urine tests
- X-rays of the chest
- Computed tomography scan of the abdomen, chest and pelvis
- Positron emission tomography (PET) scan
- Lymph node biopsy
- Lymphangiogram
- Bone marrow aspiration and/or biopsy
- Lumbar puncture.

Management

Treatment may include (alone or in combination):

1. Chemotherapy
2. Radiation therapy
3. Surgery
4. Close monitoring of blood work
5. Bone marrow transplant
6. Bone marrow examinations
7. Lumbar punctures/spinal taps
8. Antibiotics (to prevent or treat infections)
9. Supportive care (for side effects of treatment)
10. Long-term follow-up care (to determine response to treatment, detect recurrent disease, and manage late effects of treatment).

BURKITT'S LYMPHOMA (FIG. 14.36)

HISTORY

In the middle of the last century, when Denis Burkitt, a surgeon, was working in central Africa in Kampala, he noted children with grossly distorted faces, with lesions involving one or both sides of the face and upper and lower jaws, sometimes

accompanied by proptosis. He noted that some children had huge abdominal masses, sometimes accompanied by disease in the facial bones, although there was usually no lymph node involvement. This malignancy, initially thought to be a sarcoma³⁵⁻³⁷ and later established to be a lymphoma and given the name Burkitt's lymphoma, was the most common tumor in children in that area. This lymphoma was found to occur throughout tropical Africa except at high altitudes or in areas where the climate was relatively cool. Occurrence was greater in areas with greater rainfall. In 1961, Burkitt made the acquaintance of Epstein, an experimental pathologist and shared samples of the lymphoma with him. Within these lymphomas, Epstein and colleagues identified the virus that has come to be known as Epstein-Barr virus (EBV); this was the first description of a virus involved in the pathogenesis of a tumor in humans. In the setting of the florid reactive lymphoid hyperplasia that occurs in response to malaria, it was proposed that EBV could be oncogenic.³⁶

Classification According to Clinical Features

In the World Health Organization (WHO) Classification, three clinical variants of Burkitt's lymphoma are described:

1. Endemic
 2. Sporadic
 3. Immunodeficiency-associated types.
- Endemic Burkitt's lymphoma refers to those cases occurring in African children, usually four to seven years old, with a male: female ratio of 2:1, involving the bones of the jaw and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast and other extranodal sites.³⁸



FIGURE 14.36: Burkitt's lymphoma showing swelling in the right mandibular area

- Sporadic Burkitt's lymphoma occurs worldwide; it includes those cases occurring with no specific geographic or climatic association. It accounts for 1 to 2 percent of lymphoma in adults and up to 40 percent of lymphoma in children in the U.S. and Western Europe.³⁹ The abdomen, especially the ileocecal area, is the most common site of involvement; the ovaries, kidneys, omentum, Waldeyer's ring, and other sites may also be involved. Bilateral involvement of the breasts may occur in association with the onset of puberty or with lactation. Lymph node involvement is more common among adults than among children. Patients may also have malignant pleural effusions or ascites. Rarely, patients present with disease that is primarily leukemic (classified as acute lymphoblastic leukemia [ALL], L3 type in the French-American-British [FAB] Classification). Neoplastic cells are EBV positive in 15 to 30 percent of cases, or fewer in some series.⁴⁰
- Immunodeficiency-associated Burkitt's lymphoma occurs mainly in patients infected with HIV but also occurs in allograft recipients and individuals with congenital immunodeficiency. In the early years of the AIDS epidemic, several cases of Burkitt's lymphoma were described in homosexual men;^{41,42} these were the first descriptions of non-Hodgkin's lymphoma arising in association with what was later recognized as HIV infection. Information accumulated since that time indicates that Burkitt's lymphoma accounts for 30 to 40 percent of non-Hodgkin's lymphoma in HIV positive patients. In a study performed before widespread use of highly active antiretroviral therapy (HAART), Burkitt's lymphoma was estimated to be 1,000 times more common in HIV positive individuals than in the general population. Compared with other HIV positive patients with non-Hodgkin's lymphoma of the diffuse large B-cell type, those with Burkitt's lymphoma are younger, less often carry a prior diagnosis of AIDS and have higher mean CD4 counts (usually > 200 cells/ μ L). The diagnosis of Burkitt's lymphoma in an HIV positive individual often represents the first AIDS-defining criterion.^{43,44} HIV-associated Burkitt's lymphoma shares some pathogenetic features with endemic Burkitt's lymphoma. HIV infection, analogous to malaria, leads to polyclonal B-cell activation and permits poorly controlled proliferation of EBV positive B-cells. The genetic instability of the EBV^{+/+}, aberrantly regulated B-cells leads to a greater risk of *c-myc* rearrangement and then to lymphoma. HIV is not directly involved in lymphomagenesis but is indirectly involved via cytokine deregulation, chronic antigenic stimulation and decreased immune surveillance. Lymphoma often involves lymph nodes, bone marrow and extranodal sites, most often in the abdomen. Burkitt's

lymphoma occurring in transplant recipients tends to occur after a relatively long interval post-transplant (mean, 4.5 years in one series). Most patients are solid organ recipients, but recipients of stem cells are rarely affected as well. EBV is commonly but not uniformly present.

With respect to morphology, the WHO Classification describes classic Burkitt's lymphoma and two variants: Burkitt's lymphoma with plasmacytoid differentiation and atypical Burkitt's/Burkitt-like lymphoma.³⁸

- Classic Burkitt's lymphoma is found in cases of endemic Burkitt's lymphoma and most cases of sporadic Burkitt's lymphoma affecting children but in only a minority of sporadic and immunodeficiency-associated adult cases. Neoplastic cells are uniform and medium-sized (their nuclei are no larger than the nuclei of admixed histiocytes), with round nuclei and several or multiple small basophilic nucleoli. Cytoplasm is moderately abundant and with formalin fixation there may be slight cytoplasmic retraction, leading to squared-off edges between neighboring cells. The RNA-rich cytoplasm is deep blue on Giemsa or Wright stain and usually shows multiple vacuoles because of the presence of lipid, when marrow aspirates or Wright-stained touch preps are available. The mitotic rate is unusually high. Characteristically there are numerous admixed tangible body macrophages, phagocytosing abundant apoptotic debris, creating a 'starry-sky' pattern. Many cases of sporadic Burkitt's lymphoma occurring in adults have Burkitt-like morphology. Those with plasmacytoid differentiation tend to occur in association with immunodeficiency.
- Burkitt-like lymphoma and Burkitt's lymphoma with plasmacytoid differentiation, both tend to have greater nuclear pleomorphism than classic Burkitt's lymphoma and both tend to have a smaller number of more prominent nucleoli. The plasmacytoid variant has, in addition, monotypic cytoplasmic immunoglobulin. Burkitt's lymphoma, regardless of subtype, typically expresses monotypic surface IgM, pan-B-cell antigens, including CD19, CD20, CD22 and CD79a and coexpresses CD10, Bcl-6, CD43 and p53, but not CD5, CD23, Bcl-2, CD138, or TdT. The proliferation fraction is very nearly 100 percent; accordingly, the doubling time of the tumor is very short, between 24 and 48 hours. Rare cases have been reported that lack surface immunoglobulin,⁸ including some occurring in allograft recipients. The immunophenotype suggests follicle center origin for this lymphoma.

A defining feature of Burkitt's lymphoma is the presence of a translocation between the *c-myc* gene and the *IgH* gene (found in 80% of cases [t(8;14)]) or between *c-myc* and the gene for either the kappa or lambda light chain (*IgL*) in the remaining 20 percent [t(2;8) or t(8;22), respectively]. The

myc/Ig translocation may not be detected by routine cytogenetics; performing fluorescence *in situ* hybridization (FISH) or long-segment polymerase chain reaction may increase the chance of identifying the translocation. In endemic Burkitt's lymphoma, the break point in *c-myc* is more than 100 kb upstream from the first coding exon and the break point in the *IgH* gene is in the joining segment. In sporadic and HIV-associated Burkitt's lymphoma, the break point in *myc* is between exon 1 and 2 and the break point in *IgH* is in the switch (*S μ*) region, suggesting a different pathogenesis and suggesting that neoplastic transformation affects B-cells at different maturational stages for these subtypes of Burkitt's lymphoma. It should be noted however, that results have not been uniform; in a study of sporadic Burkitt's lymphoma, most presenting as leukemia, one-third of cases had chromosomal break points in the joining region of *IgH*.⁴⁰

STAGING

Staging is performed using the Ann Arbor or, more often, the St Jude/Murphy staging system.⁴⁵ Approximately 30 percent of patients present with limited-stage disease (I or II), while 70 percent present with widespread disease (stage III or IV). Patients often present with bulky disease, frequently with an elevated lactate dehydrogenase (LDH) level. Patients with any of the three clinical variants are at risk for spread to the central nervous system (CNS) and bone marrow. The bone marrow is positive in 30 to 38 percent, and the CNS is involved in 13 to 17 percent of adult cases. In a study of children with disseminated disease, 12 percent had CNS involvement and 22 percent had marrow involvement.⁴⁶

HISTOPATHOLOGIC FEATURES

- Histopathologic features represent an undifferentiated, small, non-cleaved B-cell lymphoma.
- The cells appear homogeneous with round nuclei and prominent nucleoli and presence of abnormal mitosis.
- A characteristic 'starry sky' appearance is seen due to presence of macrophages within the tumor with abundant clear cytoplasm (Fig. 14.37).

Management

1. Sporadic and immunodeficiency-associated Burkitt's lymphoma do not share endemic Burkitt's lymphoma's exquisite sensitivity to chemotherapy, so that historically the prognosis had been poor, particularly among adults.
2. Short-duration, high-intensity chemotherapy, sometimes combined with CNS prophylaxis, yields excellent survival in children: patients with localized

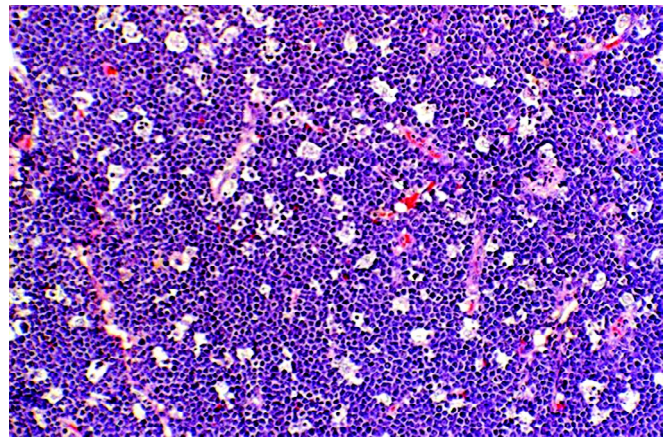


FIGURE 14.37: Burkitt's lymphoma showing 'starry sky' appearance

disease have a > 90 percent 5-year survival rate and children with widespread disease (including leukemic presentation) may achieve a > 90 percent complete response (CR) rate, with an event-free survival (EFS) rate at 4 years of 65 percent in patients with leukemic presentation, and 79 percent for those presenting with stage IV lymphoma reported in one series.⁴⁶

3. The institution of the CODOX-M/IVAC regimen (Magrath protocol)—two cycles of CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose metho-trexate and intrathecal therapy) alternating with IVAC (ifosfamide, etoposide, high-dose cytarabine and intrathecal therapy)—for high-risk disease and for those with low-risk disease (e.g. one extranodal site or completely resected abdominal disease with normal LDH), three cycles of CODOX-M, represented a major step forward in the treatment of Burkitt's lymphoma. Children and adults treated with this regimen had similar outcomes; the EFS rate at 2 years was 92 percent for the group as a whole.⁴⁷ However, there were significant associated toxicities, including frequent myelosuppression, mucositis, neuropathy and some treatment-related deaths. In addition, because of the rapid, effective tumor cell killing with this aggressive protocol, careful monitoring is required to avoid the complication of tumor lysis syndrome.
4. The Dana-Farber Cancer Institute has treated patients with a modified Magrath protocol, aimed at decreasing toxicity while maintaining good outcome. In this modification, the schedule of fractionated cyclophosphamide was altered and the vincristine dose was capped, but the dose of doxorubicin was escalated.
5. Rituximab, a monoclonal anti-CD20 antibody, may improve outcome; a study of a small series from the M.D. Anderson Cancer Center used rituximab in

conjunction with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone), with CNS prophylaxis and achieved a complete remission rate of 89 percent.

6. Novel therapies that have not been tested but could be useful include those targeted against the *c-myc* gene, DNA methyltransferase inhibitors, proteasome inhibitors, cyclin-dependent kinase inhibitors and others.
7. Among pediatric patients, a poorer prognosis is associated with age over 15 years.⁴⁸ A good prognosis is associated with resectable abdominal disease. Failure to achieve a clinical remission is a very poor prognostic sign.
8. HIV positive patients may be treated with intensive therapy but require especially close observation, with transfusion support and antibiotic therapy as needed.

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Forensic Odontology in Children

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HISTORY

The history of Forensic Odontology dates back around 4500 years. One of the first dental identification recorded was in 2500 BC when two molars linked together by gold wire were found by Junker in a tomb located at Giza.

In 49 BC, Agrippina ordered the death of her rival Lollia Paulina, who was in competition with her to be the wife of Emperor Claudius. Agrippina demanded to see Lollia Paulina's head as proof of her death, but she wasn't sure that her rival was dead until she noticed Lollia Paulina's distinctive discolored front teeth.

A new era in Forensic Odontology began in the 17th century when a body was identified from the dental details of a deceased personally known to the dentist.

In Medieval England, teeth were supposedly used to seal important documents.

Another famous foray into forensic dentistry was that of Paul Revere, who in addition to being a blacksmith was also a dentist. He helped identify Revolutionary War dead who had

been buried on the battlefield by their teeth and dental work. Revere was able to identify Dr. Joseph Warren, the man who sent him on his famous ride, because he had made him a partial denture out of silver wire and pieces of hippo tusk.

The first truly celebrated American dental identification took place in Boston in 1850. The identity of murdered physician, **Dr George Parkman**, was established through dental evidence. The murderer, Dr. John Webster, a Harvard professor, had attempted to dispose of the body by incineration in his laboratory furnace. However, a partial denture and a portion of jaw were recovered from a privy where they had been disposed of after burning. Although one dental expert testified that in his opinion it was unlikely that a dentist would remember the dentistry from previous patients, the jury believed Dr. Nathan Cooley Keep who demonstrated how the partial denture and recovered bone fragments fit a cast of Dr. Parkman's jaw and jury was convinced. Dr. Webster was hanged.

The first case in which a great number of victims died occurred in Paris in 1897. A fire during charity bazaar resulted in 126 fatalities. After routine methods of identification of the

time (visual and personal effects succeeded for less than 100 of the victims), dental identification was used.

Dr Oscar Amoedo presented a paper about identification of the case in 1897, published in *Dental Cosmos* in 1897, and authored a textbook first published in 1898 on the field of Forensic Dentistry.¹ Since that time, dental identification has become an important part of any identification process when multiple deaths occur.

A recent review of appellate decisions, presented by Judge Haskell Pitluck of Illinois (1989) revealed 132 American cases, in the history of dental involvement in the field of bite mark analysis.²

Battered child syndrome entered the lexicon of America in 1962, publicizing a problem that dates back to early civilizations.³

German dictator Hitler and in recent times Pakistani President General Zia-ul-Haq were identified only with the help of dental evidence.

The Royal Mail Ship (RMS) 'Titanic' had a brief and inglorious history that culminated with her striking an iceberg and sinking on April 15, 1912, while on her maiden voyage. The teeth were instrumental in determining the identity of an 'Unknown Child'.

Recently, on 26th December, 2004, Tsunami caused devastation and loss of life around Indian Ocean. 1,474 deceased have been identified. Dental comparison has been the primary identifier in 79 percent of cases and a contributor in another 8 percent, a total of 87 percent.

TERMINOLOGIES

FORENSIC SCIENCE

Forensic science is defined as the study and practice of the application of science to the purpose of law.⁴

FORENSIC MEDICINE

Forensic medicine is defined as the science of medicine as related to the law.⁵

FORENSIC ODONTOLOGY^{5,6}

Forensic odontology is the branch of odontology, which deals with the proper handling and examination of dental evidence and with the proper evaluation, and presentation of dental findings in the interest of justice.

FORENSIC ODONTOLOGY

Forensic odontology or forensic dentistry is one of the most unexplored and intriguing branches of forensic sciences. It primarily deals with identification, based on recognition of

unique features present in an individual's dental structures. Forensic dentistry plays a major role in identification in manmade or natural disasters – events that result in multiple fatalities that may not be identifiable through conventional methods such as fingerprints (Figs 15.1 and 15.2).

Major fields of forensic odontology:

- Civil non-criminal.
- Criminal:
 - Identification of persons from their dentition or teeth.
 - Dealing with bite marks identification.
- Research.

Forensic odontology has three major areas of utilization:

1. Diagnostic and therapeutic examination and evaluation of injuries to jaws, teeth and oral soft tissues;



FIGURE 15.1: Forensic anthropologists can help to identify skeletonized human remains, such as those found lying in shrub in Western Australia, circa 1900-1910



FIGURE 15.2: Searching for body fragments of badly burnt bodies at the site of a mass disaster

2. Identification of individuals, especially casualties in criminal investigations and/or mass disasters; and
3. Identification, examination, and evaluation of bite marks which occur with some frequency in sexual assaults, child abuse cases and in personal defense situations.

Forensic odontologists delve into:

- Identifying unknown human remains through dental records and assisting at the location of a mass disaster.
- Eliciting the ethnicity and assisting in building up a picture of lifestyle and diet of skeletal remains at archaeological sites.
- Determining the gender of unidentified individuals.
- Age estimation of both the living and the deceased.
- Recognition and analysis of bite marks found on victims of attacks and on other substances such as foodstuffs.
- Presenting evidence in court as an expert witness.

Classically, forensic dentistry can be considered a subspecialty of oral and maxillofacial pathology. This is analogous to the relationship in medicine between forensic pathology and pathology. The requirements of forensic dental fieldwork, however, often demand an interdisciplinary knowledge of dental science. This has resulted in other dental specialists and general dentists joining oral and maxillofacial pathologists in providing legal authorities with dental expertise.

ROLE OF THE PEDODONTIST IN FORENSIC ODONTOLOGY

A pedodontist plays an important role in forensic odontology by applying his expertise in the following areas:

- Mass disaster.
- Child abuse and neglect.
- Accidental and non-accidental oral trauma.
- Dental fraud.
- Age determination.
- Bite marks.
- Lip prints.
- Poisoning.
- Dental records.

In recent years, the accelerated application of Scientific Methodology to Criminalistics and to the Field of Law has led to the creation and subsequent recognition of a multitude of special study disciplines, which comprise the forensic sciences, thus forensic dentistry. The focus of forensic dentistry occupies a primary role within the total spectrum of methods applied to medicolegal identification.

ORAL AUTOPSY PROTOCOL

Autopsy, also known as necropsy or postmortem, involves examination of the deceased, usually with dissection to expose

the organs, to determine the cause of death. Autopsy has a systematic protocol starting with critical examination of the external features of the body such as gender, ethnicity, build, wound, scars, tattoos and body piercing. Photographs, radiographs, fingerprints, fingernail scrapings and hair samples may be obtained according to the requirements.

The dental autopsy is a very important part of the investigative procedure, which ideally will lead to identification. A forensic odontologist may be required to perform a dental or oral examination on a body in one of the following categories:

Normal: Everything is normal except that the subject is dead. Rigor mortis complicates the accessibility.

Rigor mortis time frames after death are:

- < 12 hours – Commencement of rigor mortis
- 12 hours – Complete rigor mortis
- 18-36 hours – Beginning to disappear
- 48-60 hours – No longer present.

Decomposed: Decomposition can be classified into primary or advanced. If the body or specimen is refrigerated, the odor remains minimal. Resected specimens will deodorize if they are soaked in formalin for 30 minutes or more.

Mutilated: The bodies in high-impact accidents, such as air crash would fit into this category where one finds tissue and bone destruction with fragmentation.

Burned: Due to severe burning, soft tissue may get scraped off the bone to provide easier access to the oral cavity and the teeth. Bones may get fragile, they can be strengthened before sectioning by spraying them with artist's clear matte finish. The material is completely radiolucent, so radiographs are as clear as they would be without the coating. An alternate method is to expose the anterior dentition carefully and, using an etching brush, coat the fire-damaged teeth with cyanoacrylate glue.

Skeletonized: The bones are without soft tissue or only remnants remain in a few areas. This is the easiest to deal with in regard to accessibility for examination, radiographs, photographs and study model impressions.

AUTOPSY METHODS⁷

(After securing proper permission)

Body beyond recognition (autolysis, fire, mutilation, etc.)

- Photographs (properly identified), *in situ*.
- Incision—Corner of mouth to tragus of the ear.
- Disarticulation of mandible or saw cuts posterior to third molar area (Stryker electric saw or by bone saw).
- Cuts into maxillary sinuses above post apices of teeth and dissection of maxilla.
- Wrap specimens in plastic or soak in 10 percent formalin and bleach solution until fixed and odor controlled. Check the specimens twice daily to prevent demineralization.

- Radiographs—Periapical films taped to area with decreased settings on machine; or, split maxilla and mandible in midline and place on ring stand using occlusal film.
- Photograph specimens.
- Chart all dental findings.
- Return specimens to remainders of body unless written permission is granted to retain custody.

VIEWABLE BODY (no mutilation, autolysis, etc.)

1. Photographs (properly identified) *in situ*.
2. Utilize mouth props to open mouth or wait until rigor mortis disappears. If prying methods are used to open mouth, be careful not to fracture teeth.
3. Intraoral photographs (properly identified).
4. Radiographs—Periapicals: or, tape occlusal film on cheek parallel to the alignment of the posterior teeth or to the crest of the alveolar ridge if the jaw is edentulous. The central ray (dental or portable medical X-ray machine) is directed from a point below the inferior border of the mandible on the side opposite to the first molar region of the side to be examined. Distortions are present in this view.
5. Charting—Use checklist system to ensure complete oral examination.

JAW RESECTION METHODS

Several terms are used for this procedure, such as ‘resect’, ‘remove’, ‘disarticulate’ and ‘exenterate.’

Two methods for jaw resection may be used:

1. A mouth prop is required to hold the mandible in the open position. This provides good access to all surfaces of the teeth. Incision can be given on both sides, from each corner of the mouth to the posterior border of the ramus of the mandible. It should be in line with occlusal plane and through the cheek to the oral cavity. Then make vertical incision at either ends of the horizontal one, at posterior border of ramus of the mandible. Dissect the tissue superiorly beyond the apices of the longest teeth so that it also exposes the lower part of the lateral wall of maxillary sinuses and outer surface of the ramus.
2. Second method used is Keiser-Nielsen’s method, 1980. In this method, a horseshoe-shaped incision is made below the inferior edge of the mandible, so that postoperatively, suture lines will not be visible. Alternatively, dissection may be started from the upper chest area where the forensic pathologist’s autopsy began, extending the incision laterally on both sides to the hairline. This allows for the careful repositioning of the flap and esthetic packing of the area where the jaws are missing in order to return the facial features as close as possible to the original contours.

After removal, jaws can be placed in a heavy-duty plastic bag containing a swab soaked in formalin and sealed with wire or tape. Then detailed examination should be carried out. Ideally, jaws can be returned to the mortuary to be placed with the body if there is a positive identification.⁸

Feriera and associates presented a technique of oral autopsy, which included means of accessing the oral cavity in burned human remains. Since teeth may be brittle in burned cases, they need to be reinforced with cyanoacrylate cement, polyvinyl acetate or clear acrylic spray paint prior to examination. Access for radiography in incinerated bodies can be obtained by removing the tongue and contents of the floor of the mouth in a “tunneling” fashion from beneath the chin.⁹

SCIENTIFIC METHODS OF IDENTIFICATION

In the forensic sciences, a great deal of effort is spent on the identity or confirmation of identity of the victims and perpetrators. Forensic identifications by their nature are multidisciplinary team efforts relying on positive identification methodologies as well as presumptive or exclusionary methodologies.¹⁰

Legal certification of an individual’s identity is based on a number of parameters most of which are centered about the individual’s appearance and personal effects. As such, many people are buried or cremated based on a visual identification or other presumptive identification methods. Where possible, a positive identification is preferred to a presumptive identification in such medicolegal cases.

Positive identification traditionally involves a comparison of pre- and post-mortem data, which are considered unique to the individual. These methods include: (1) Dental comparisons; (2) Fingerprints, palm prints and footprints; (3) DNA identifications; and (4) Radiographic superimpositions (vertebrae, cranial structures including frontal sinuses, pelvic structures, bone trabeculae and prostheses).

Presumptive identifications include: Visual recognition, personal effects, serology, anthropometric data, and medical history which do not usually identify unique characteristics of the individual but rather present a series of general or class characteristics which may exclude others based on race, sex, build, age, blood group, etc. Most positive identifications today are based on dental examinations and fingerprints and are fundamental procedures in medicolegal death investigations including mass disasters.¹⁰

TECHNOLOGIES FOR AGE DETERMINATION

Dental age estimation makes use of morphologic, radiographic, histologic, and biochemical methods to examine age dependent changes in teeth.¹¹

ASPARTIC ACID RACEMIZATION

Aspartic acid racemization has been used for age estimation based on its presence in human dentin. Most protein components of body consist of L-amino acids, whereas D-amino acids have been found in bone, teeth, brain, and the eye's crystalline lens. D-amino acids are believed to have a slower metabolic turnover and subsequently a slower decomposition rate. Aspartic acid has the highest racemization rate of all amino acids. In 1976, Halfman and Bada used this information to study age estimation by comparing D/L aspartic acid dental ratios in 20 subjects with good results ($r = 0.979$).¹⁰

A high coronary D/L ratio was noted in the younger age group, decreasing with age presumptively due to environmental changes. This determination technique is based on a linear regression equation: $\ln(1+D/L) / (1-D/L) = 2K(\text{Aspartic})T + \text{Constant}$, where $K = 1\text{st order kinetics}$ and $T = \text{actual age}$. Subsequently, they found that better age estimations could be achieved with fractionating the total amino acid fraction (TAA) into an insoluble collagen fraction (IC) and a soluble peptide fraction (SP). SP had higher concentrations of aspartic acid and glutamine, both hydrophilic acids. So, this has the most reliable age estimation because of a high racemization rate roughly three times that of TAA.¹⁰

DENTAL STRUCTURE IDENTIFICATION

Scanning electron microscopy (SEM) with and without energy-dispersive X-ray (EDX) analysis has been used to identify teeth by dentinal tubules and evidence of previous restorations, especially in incinerated remains. Use of SEM with EDX provided a profile of elements present which may identify a particular type of dental material. *Fairgrieve* in 1994 reported a similar case involving SEM on incinerated teeth to evaluate parallel striations in tooth enamel and dentine as evidence of previous dental restorations.¹²

Smith in 1990 reported the application of SEM with EDS (Energy Dispersive X-ray Fluorescence Spectrometry) analysis on MIA remains from Southeast Asia based on examination and analysis of proximal facets.¹³ *Smith* also noted that this preliminary study indicated that it was possible to detect restorative material residue on the proximal surfaces of unrestored teeth and indicate the antemortem existence of a restoration on the adjacent tooth surface. This knowledge could be valuable in presumptive identifications where the teeth with critical restorations were not recovered with the primary remains, but teeth proximal to those with restorations were present.

SORTING BY METAL RATIOS

In 1986, *Fulton et al*,¹⁴ reported on the use of metal ratios in the reassociation of scattered and mixed human bones. The

magnesium/zinc ratio was the most reliable, with zinc/sodium, magnesium/sodium and chromium/sodium ratios useful for supplemental comparative studies. Furthermore, individual trace elements, such as, arsenic complement this sorting process effort. The authors concluded that this ancillary procedure did not provide sufficient individuality to be used alone, but was a valuable adjunct to standard anthropological techniques typically used for sorting commingled remains.

SEROLOGICAL PARAMETERS

Forensic serology has been applied to odontological investigations with reasonable success. In dental pulps, ABO blood groups and serum proteins Gm, Km and Gc are present as well as eight polymorphic enzymes (PGM, PGD, ADA, AK, EsD, Fuc, DiA3 and transferrin).

Kido et al in 1993, reported on the use of transferrin C subtyping by isoelectric focusing electrophoresis in dental pulps. Sensitive immunoblotting techniques had previously identified transferrin subtypes in urine, blood stains and semen. The Kido et al study showed good correlation between serum and dental pulp specimens.¹⁵

In 1993, Lopez-Abadia and Ruiz de la Cuesta reported a simplified method for phenotyping alpha-2-HS glycoprotein in serum, blood stains and dental pulp using isoelectric focusing electrophoresis on neuramidase-treated specimens, with excellent results.¹⁶

SALIVA: AN IDENTIFICATION TOOL

Saliva offers several routes of inquiry. Identification of inorganic anions such as thiocyanate or nitrites and polymorphic enzymes such as alkaline phosphatase and amylase, are directed towards its identification in bite marks. Further individualization is directed towards classical serological parameters including the detection of blood groups, serum polymorphic enzymes and polymorphic studies unique to saliva based on electrophoretic variation of isoenzymes of hexose-6-phosphate dehydrogenase (Sgd), amylase, acid protein (Pa), basic protein (Pb) double band protein (Db), and proline rich protein (Pr). In addition to ABH, Lewis and Sda antigens, a number of serum polymorphic isoenzymes are present in saliva: alkaline phosphatase, amylase, esterases, G-6-PD, and parotid peroxidase (SAPX). Saliva also contains an interesting polymorphic protein system based on parotid glycoproteins; most, if not all, are acidic and proline rich. Both Gm and Km proteins are present and have been used for racial determinants. Harrington et al 1988, described their efforts to detect hemagglutinins in dried saliva stains for comparison with blood typing.¹⁰ Salivary drug detection use has been explored, especially in monitoring therapeutic drug concentration and detection of impaired drivers in a relatively non-invasive fashion. *Peel et al* 1984, found measurable quantities of drugs

in saliva extracted with methanol and analyzed by EMIT (enzyme multiple immunoassay technique) and gas chromatography / mass spectrophotometry.¹⁰ A number of drugs such as phenobarbital, amphetamine and morphine have been detected in saliva and saliva stains by radioimmunoassay (RIA) by a number of investigators. Smith described similar studies in bloodstains for drug content.¹⁷

PALATAL RUGAE PATTERN

Palatal rugae, also called as plicae palatine transversae and rugae palatina refer to ridges on the anterior part of the palatal mucosa on each side of the midpalatine raphe, behind the incisive papilla. Palatal rugae are well protected by the lips, cheek, tongue, buccal pad of fat and teeth in incidents of fire and high-impact trauma. Rugae patterns, like teeth, are considered unique to an individual. They do not change shape with age and reappear after trauma or surgical procedures (Fig. 15.3).

Palatal rugae classification has spanned almost 100 years; the one suggested by Lysell is quoted most often.¹⁸ He measured rugae in a straight line from the terminus at the lateral and categorized them into three:

1. Primary rugae (> 5 mm)
2. Secondary rugae (3-5 mm)
3. Fragmentary rugae (2-3 mm).

(Rugae < 2 mm is not taken into consideration).

Thomas and Kotze have further detailed the various patterns of primary rugae. These include branched, unified, crosslinked, annular and papillary.¹⁹

Sunita Kapali et al in their study observed that the length of rugae increased significantly with age, but the total number of rugae remained constant. They also found ethnic variation in rugae, for example, straight rugae were common in Caucasians while wavy forms were common in Aborigines.²⁰

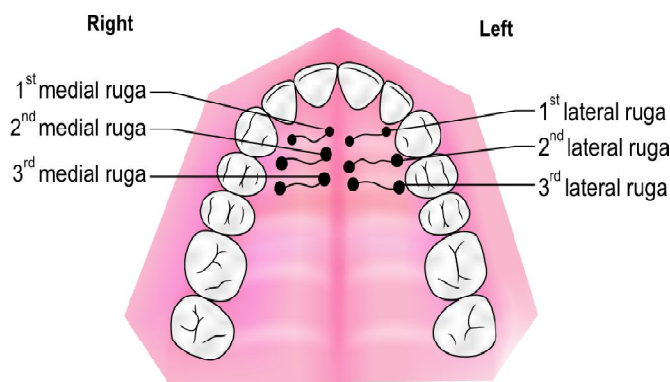


FIGURE 15.3: Landmarks on a dental cast, showing 1st, 2nd and 3rd rugae with their medial and lateral points

Apart from problem of intra-observer discrepancies in reading rugae patterns, there is no doubt that even greater discrepancies could exist between observers. The existence of this unreliability brings into question the present usefulness of descriptive rugoscopy in the fields such as forensic science.²⁰

KS Limson and R Julian assess the feasibility of palatal rugae patterns for identification with the aid of computer and software program known as RUG FP-ID Match. In circumstances where the identification of an individual by fingerprints or dental record comparison is difficult, palatal rugae may be considered as an alternative source of comparative material. Technological advances now available to the forensic dentists such as computers, image capturing devices and the ability to transfer information quickly have simplified the task of human identification in deceased individuals as well as in mass fatality situations. In their study of about 250 subjects, the success rate of 92 to 97 percent was obtained.²¹

LIP PRINTS AND THEIR USE FOR IDENTIFICATION

This idea was first suggested by *Le Moyne Snyder in 1950* in his book Homicide Investigation. Santos et al in 1960 reported that wrinkles and grooves found on the lip could be divided into simple and compound types. Suzuki in his study found none of his participants to have the same lip groove pattern.²²

Tsuchihashi named the wrinkles and grooves visible on the lips as 'sulci labiorum rubrorum'.²³ The imprint produced by these grooves is termed as 'lip prints', the examination of which is referred to as 'cheiloscopy'. These grooves are heritable and are supposed to be individualistic. Cheiloscopy is used in the same manner as fingerprints.

It is analogous to bite marks analysis.

Lip prints were first classified by *Martin Santos, 1966*, thus:

Simple wrinkles

- Straight line
- Curved line
- Angled line
- Sine-shaped curve.

Compound wrinkles

- Bifurcated
- Trifurcated
- Anomalous.

Tsuchihashi later proposed a separate classification, dividing the pattern of grooves into six types:

- Type I: Clear-cut vertical grooves that run across the entire lip.
- Type I': Similar to type I, but do not cover the entire lip.
- Type II: Branched grooves.
- Type III: Intersected grooves.
- Type IV: Reticular grooves.

Type V: Grooves that cannot be morphologically differentiated.

Lip prints are usually left at crime scenes and can provide a direct link to the suspect. In recent years, lipsticks have been developed that do not leave any visible trace after contact with surfaces such as glass, clothing, cutlery or cigarette butts and have been called persistent lip prints. Although invisible, these prints can be lifted using materials such as aluminium powder and magnetic powder.

Types of lip prints (Fig. 15.4):

1. Vertical
2. Branched
3. Intersected (diamond grooves)
4. Reticular.

Minor differences have been observed between right and left sides and between upper and lower lips.

Lip prints on drinking glasses, facial tissues, magazines and undergarments have been used as evidence.

RECORDING LIP PRINTS

There are a number of ways:

1. On a non-porous flat surface such as mirror, they can be photographed, enlarged and overlay tracings made of the grooves.
2. Photographed directly with no medium and tracings made, but this requires correct lighting.
3. Rouge can be applied to the lips and then the lips are photographed.

Images are then observed through magnifying glass and traced onto cellophane. Lip prints can be developed using a

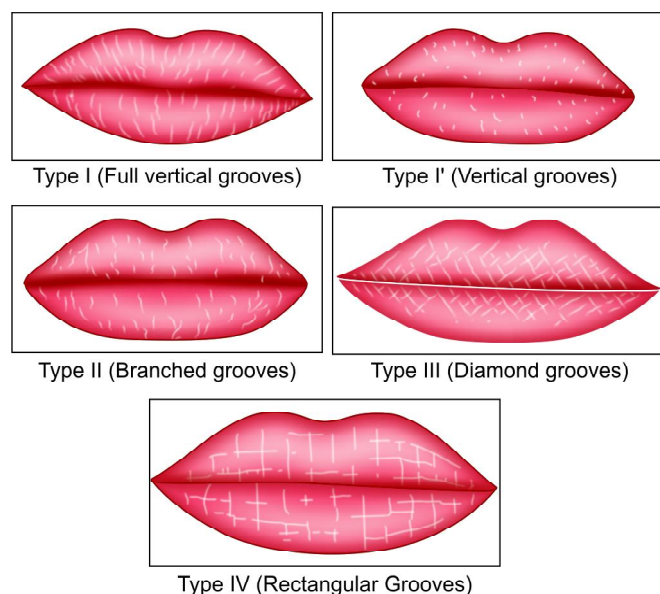


FIGURE 15.4: Classification of lip prints

number of different powders or cyanoacrylate and photographed.

Pattern on lips is quite mobile and print may vary in appearance according to pressure, direction and method used in making the print. Lipstick amount applied may affect outcome.

Although lip prints have been used in court in isolated cases, there needs to be far more research to support the claim of uniqueness attributable to any such evidence. Actual use of lip prints in court is rare; however, its acceptance is debatable.²²

RECONSTRUCTION OF THE FACIAL TISSUE

Positive identification is achievable when the skull and facial bones are used as a foundation to reconstruct the facial soft tissues. Three-dimensional computer images, computed tomography (CT) images and radiographs have been used in the replication of the face of a 5000-year-old person whose remains were removed from glacial ice on the Austrian and Italian border.²⁴

With knowledge of the anatomic relationships between the skull and face, antemortem facial photographs or radiographs can be superimposed and matched with the skull. Video superimposition with two television cameras and an electronic mixing device has been used successfully in overlaying a photograph of a human face on an image of a skull for identification (Fig. 15.5).^{24,25}

DNA IDENTIFICATION

Dental identification takes advantage of the polymorphic nature of the hardest tissues in the body—precisely those structures, which are most likely to remain available for identification purposes. Although dental structures are more likely to survive traumatic and decompositional changes than other traditional means of identification such as fingerprints, scars, facial appearance, etc. DNA has a still greater likelihood of survival.

A common obstacle to fingerprint and dental identification is the lack of antemortem data for comparison. The common

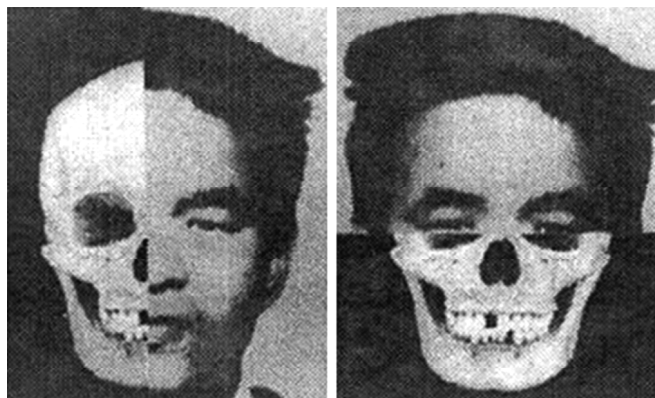


FIGURE 15.5: Reconstruction of facial tissue

availability of families as sources of reference material for comparison purposes is a particularly important aspect of DNA identification.

THE DNA MOLECULE

The basis for all inheritance is found in the DNA genome of cells. This information is coded within the chemical structure of the DNA molecule or more accurately, the set of DNA molecules known as the genome. Nucleotide bases are arranged in specific sequences within the chemical structural scaffolding. Only four bases (adenine, cytosine, guanine and thymine) make up the genetic alphabet that produces the words, sentences, paragraphs and chapters, which are eventually read into proteins that comprise biological organisms. These bases are present in pairs in a complementary fashion to form base pairs, such that every A is paired with a T, every C with a G, and vice versa.

Stability of DNA: DNA is a robust molecule which can tolerate a remarkable range of temperature, pH, salt, and other factors that destroy classical serological markers. This ruggedness allows DNA longevity and has permitted DNA typing of Egyptian mummies and 30-million-year-old insects preserved in amber.²⁶

DNA POLYMORPHISMS

This can be length-based or sequence-based. Length-based polymorphisms are a characteristic of repetitive DNA that generally does not code for any protein (so-called 'junk' DNA). DNA fragments vary in size between individuals due to the presence of variable numbers of tandem repeats (VNTRs), i.e.: core of 7 bases may be repeated 3 times in one individual or 12 times in the next individual. Traditional restriction fragment length polymorphism (RFLP) analysis, as is commonly associated with the DNA testing in crime labs, involves cut fragments (restriction fragments), which include internal VNTR region (loci) and thus vary in fragment length. VNTR fragments can also be amplified instead of cut, then called as amplified fragment length polymorphisms (AmpFLPs).

DNA identity information is found not only in fragment length variation, but also within the DNA sequence of similarly sized DNA fragments. Sequence polymorphisms consist of difference changes in one or more bases in a DNA sequence at a particular location in the genome. Sequence variations can manifest as regions of alternative alleles or base substitutions, additions or deletions. Most sequence polymorphisms are mere point mutations. Sequence polymorphisms can be detected by DNA probes or by direct sequencing.²⁶

DNA IDENTIFICATION METHODS

DNA testing is far superior to those other tissue-typing techniques for a variety of reasons. DNA is the basis for all

blood group types, red cell antigens and protein isoenzymes. Due to the degeneracy of genetic code, there will be more polymorphisms than the resultant phenotypes. The discriminatory power of DNA is far greater than any set of traditional markers including HLA typing. It can be performed on any tissue or fluid. DNA is less susceptible to environmental insults so can be performed on far older specimens.^{27,28}

RFLP Methods (Restriction Fragment Length Polymorphisms)

This DNA typing method that was first described and most commonly employed by many crime labs initially is known as restriction fragment length polymorphisms (RFLP) analysis.

The six steps in RFLP testing include:

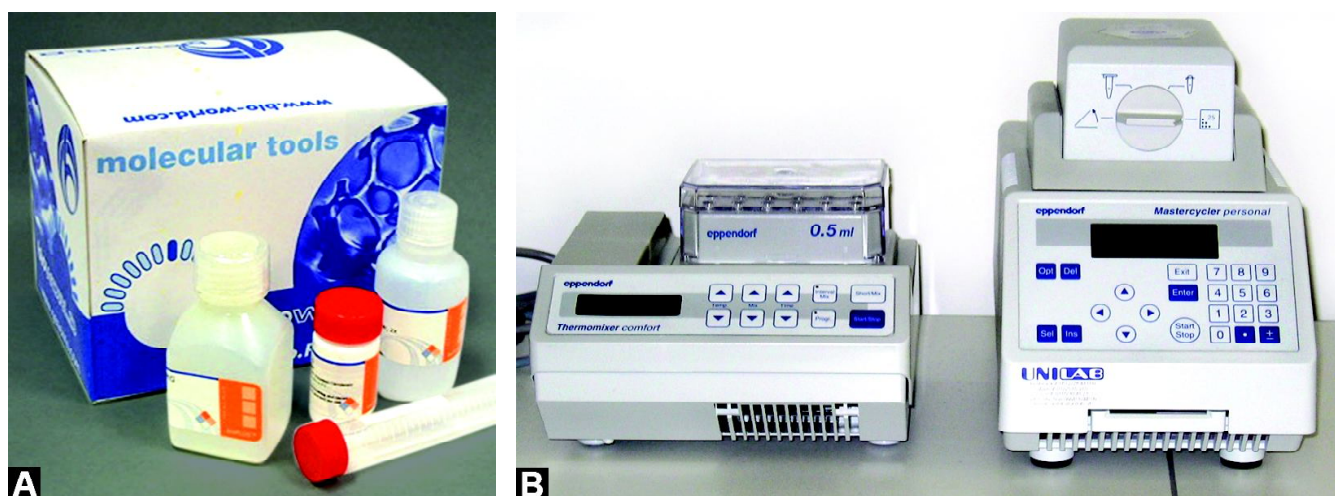
1. Extraction of DNA from a biologic source.
2. Cutting the DNA into relatively small fragments at specific sites with 'restriction enzymes'.
3. Separating the fragments by size using agarose gel electrophoresis.
4. Transferring and immobilizing the separated DNA fragments onto a nylon membrane.
5. Denaturation of the DNA into single strands and hybridization to radioisotopically-labeled probes (small fragments of single-stranded DNA).
6. Autoradiography in which an X-ray film is placed over the membrane for several days resulting in exposure of the film at the point of the probe.

RFLP testing is often called as 'Southern blotting' because the DNA transfer technique was first described by Professor Southern. Typically, RFLP testing will take several weeks to perform. For every probing, the membrane is stripped off the previous probe and rehybridized and autoradiography performed anew. However, alternatives to radioisotopic labels now exist, particularly chemiluminescent and fluorescent probe labels, which permit much faster testing.

Unfortunately, RFLP is not useful where the DNA is degraded; so, RFLP testing is of limited value in testing cadaver tissue for identification of human remains, unless the remains are fresh.²⁶⁻²⁸

Polymerase Chain Reaction (PCR) Methods (Figs 15.6A and B)

It is a method of copying or 'amplifying' a particular segment of DNA. A few strands or a single strand of DNA can be used to reproduce millions of copies of target DNA fragments. Kary Mullis was awarded the Nobel Prize in 1993 for the discovery of the PCR process, which has led to a revolution in the life sciences. PCR amplification is a sample preparation technique, which enables further testing to detect various polymorphisms. Nonamplified DNA becomes undetectable against the amplified



FIGURES 15.6A and B: PCR kit

background target sequence. PCR testing is sensitive, quicker, less labor intensive and less tedious than RFLP testing. It is also used for degraded specimens because only a few copies of relatively short segments need to remain intact. However, PCR testing is susceptible to inhibition and the potential for cross contamination.²⁷

Human X and Y chromosome alpha-satellite sequences lying within higher order repeats were amplified by the polymerase chain reaction (PCR) in genomic deoxyribonucleic acid (DNA) isolated from blood, bone, and several other tissues and specimens of potential forensic science interest. X and Y sequences could be coamplified under some of the PCR conditions employed. X and Y sequence amplification can provide information about the sex of origin. Amplification of the X, H, and D17Z1 sequences was found to be primate-specific among the common animals tested and can thus provide species of origin information about a specimen. The authors suggest that amplification of X and D17Z1 or H sequences might provide “relaxed” and “stringent” controls for appropriate PCR amplification tests on forensic science specimens. Testing was carried out using PCR protocols that employed *Thermophilus aquaticus* (Taq) and *Thermus flavus* (Replina) thermostable DNA polymerases.²⁹

Dot/Blots

Sequence information can be obtained through the use of DNA probes. A DNA probe is a small piece of single stranded DNA (oligonucleotide) which will bind to another single-stranded DNA with the complementary sequence. A sequence specific oligonucleotide (SSO) probe, also known as an allele-specific oligonucleotide (ASO) probe, is a single-stranded DNA

fragment. Commercial kits, i.e. DQ-alpha and Poly-Marker systems, are based on a dot/blot format for SSO typing and are currently in use by many crime labs. The resultant dot/blot strip has a series of spots that turn blue if the reaction is positive and in this way give a series of yes/no results. These dot/blot tests are quite rapid and work reasonably well despite sample degradation, but do not harbor the same discriminatory power as RFLP tests.²⁶

The sex determination of bloodstains was performed using a human Y chromosome-specific (DNA) fragment of 1.9 kb length as a hybridization probe. The DNA samples were taken from 1- and 4-week-old bloodstains of males and females, respectively. Strong signals with male DNA were observed by Y-probe, while faint signals with female DNA were detected. In addition, clear signals were observed in the extract samples from male bloodstains (16-week-old) on paper. Dot hybridization of the Y-probe would be widely applicable to studies on sex determination of medicolegal materials such as blood, bloodstains, teeth, and cadaverous parts.³⁰

AmpFLPs and STRs

Dinucleotide repeats are not generally used in forensic laboratories due to the artifactual production of so-called “shadow” and “stutter” bands.

The shorter STR fragments are generally preferable for a variety of technical reasons. These STR systems work well despite significant degradation and are quite amenable to automation. Sufficient numbers of STR systems can be performed to achieve discriminatory powers similar to current RFLP testing. The British and Canadian crime labs are moving towards using STR systems exclusively.²⁶

TYPES OF DNA

Pretty and Sweet have pointed out the use of two types of DNA. The first is called genomic or nuclear DNA. This is located in the nucleus of the cells and is commonly used in forensic cases. The second, known as mitochondrial DNA (mt DNA), is present in the mitochondria of cells. Bender and associates point out that a major advantage of mt DNA is that each cell has a high copy number of mt DNA, e.g.: epithelial cells contain 5000 mt DNA molecules. Also, mt DNA is exclusively inherited from the mother.³¹

Mitochondrial DNA (mt DNA)

DNA is not only present in chromosomes in the nuclei of the cells, but also is present in mitochondria of cells. Mitochondria are known as the powerhouses of the cells as they are the primary machinery for accomplishing oxidative mechanism. Tens, hundreds or even thousands of mitochondria are present within a single cell and each mitochondrion contains thousands of copies of mitochondrial 'DNA particles' of 16000 bp (base pairs) mt DNA sequence can be obtained when the nuclear DNA type cannot.

No significant regions of repetitive DNA exist in mt DNA, only sequence polymorphisms are typed. The region of mt DNA which is analyzed for human identification is the noncoding region known as the displacement loop (D-loop) or control region. A unique feature of mt DNA is its mode of inheritance—one half of the nuclear DNA is from the mother and one-half from the father. Mitochondria are inherited in a strictly mother-to-child manner; there is no paternal contribution. Accordingly, mt DNA can be traced through a family via maternal lineages for many generations. It has great application to severely decomposed or skeletonized remains. Very few laboratories are performing this kind of testing at this point in time.²⁶

SPECIMEN SELECTION, COLLECTION AND PRESERVATION

DNA can be isolated and tested from virtually any postmortem tissue, although after death DNA, will undergo fragmentation by autolytic and bacterial enzymes, specifically DNases. Nevertheless, the sequence information is still present within the DNA fragments and therefore, the information is not completely lost despite the fairly extensive fragmentation, which occurs from decomposition. Traditional RFLP testing will require non-degraded high molecular weight DNA, whereas PCR-based analysis can be performed on degraded samples and mt DNA can be obtained from skeletal remains when nuclear DNA cannot.

In relatively fresh cadavers, unclotted blood is the preferable source of DNA. Although heme is an inhibitor of PCR, laboratories are accustomed to blood as a DNA specimen and although only white blood cells carry the DNA, ample DNA is present for testing. Due to the settling out of white blood cells, clotted blood may not be a good source of DNA. Blood is a good culture medium and bacterial growth may render blood samples useless. Any tissue can be used successfully for DNA typing purposes. Brain tissue is said to be a particularly good source of DNA in intermediate postmortem time periods. Hard tissues (bone and teeth) are the best source of DNA in cases of advanced decomposition.

PRESERVATION

The specimens should be kept cold or preferably frozen (repeated freezing and thawing is not good). Desiccation, even simple air-drying, may be adequate for storage of some DNA specimens, e.g. bloodstains and bone.

Formalin fixed tissues are not optimal, but can be used for PCR-based DNA testing. No tissues or biologic fluids should be discarded as inadequate without first attempting DNA testing. Great care should be taken to prevent specimen contamination. Specimens should be collected with gloves and pristine instruments. Fresh tissues should be collected by an incisional biopsy technique where possible.²⁷

TEETH AS EXCELLENT SOURCE OF DNA

Since teeth can resist extreme conditions, Pretty and Sweet state that teeth are an excellent source of DNA. One may doubt ability of the teeth to yield sufficient quantities of DNA for analysis, particularly under the circumstances when the post-mortem interval ranges from a few months to years. However, a routinely applied technique in forensic investigations, polymerase chain reaction (PCR), allows amplification of even highly degraded DNA.³¹

DNA is present in the vascular pulp of the tooth, but it is also found throughout the tooth in varying levels, particularly in the odontoblastic processes, accessory canals and cellular cementum. Most information necessary for traditional dental identification is present in the crown (enamel and dentin) of the tooth. Consequently, a tooth can be sectioned horizontally through the cervical root subjacent to the CEJ, preserving most restorations for traditional dental comparison purposes.²⁶

Sweet and Hildebrand have advocated a method known as cryogenic grinding for extracting DNA. This involves cooling the whole tooth to extremely low temperatures using liquid nitrogen and then mechanically grinding it to fine powder. The major drawback of cryogenic grinding is that the tooth needs to be completely crushed.³²

REFERENCE SAMPLES/DATABASES

Reference specimens for DNA testing are generally available from family members. Specimens from the spouse and children will permit ‘reverse paternity’ testing using nuclear DNA probes. Specimens from parents and siblings will permit identification, particularly in closed populations. Mt DNA analysis must be performed on maternal kindred (mothers, siblings, children only in the case of a female); it can be performed even in distant relatives (maternal aunts and uncles, children of sisters).

Primary DNA specimens of individuals may be available from toothbrushes, biopsies or tissue slides archived in a hospital’s pathology department, from stored blood donations, from licked envelopes and stamps, or in case of mt DNA from locks of baby hair or clippings from an electric shaver.¹⁰

Future DNA testing technologies will permit high-volume, low-cost testing, significant in mass disaster.

IMPORTANCE OF BLOOD GROUP DETERMINATION

In 1900, **Landsteiner** noted that blood from one person mixed with the blood from another produced visible clumping of red blood cells. This observation led to discovery of the ABO groups and opened a new and complex field of study (Fig. 15.7).

The use of blood group substances in medicolegal examinations is based on the fact that once a group is established in an individual it remains unchanged throughout his life.

BLOOD GROUP SYSTEMS

The term “blood groups” is applied to inherited antigens detected on the red blood cell surface by specific antibodies. Blood groups within a blood group system are inherited by single or multiple allelic genes. At present more than 250 blood



FIGURE 15.7: Karl Landsteiner, the discoverer of various blood groups

group substances or antigens have been found on the red cells. Some of these antigens frequently occur whereas others are rare, e.g. H antigen is present in 99.9 percent of the population whereas B3 is present in less than 0.1 percent.³³

The most important system is the ABO system, which is of major importance in blood transfusion and tissue transplantation. The well known Rhesus (Rh) blood group system is important because of its role in hemolytic diseases of the newborn (erythroblastosis fetalis). Other well known systems are MN, Lewis, Kell, P, I, Kidd, Lutheran and Duffy systems.³³

INHERITANCE OF BLOOD GROUP SYSTEMS

Within a few years after the ABO system was described, it was established that blood groups are inherited in accordance with Mendelian laws and are generally inherited as simple Mendelian dominant characters.

The laws of inheritance of red blood antigens have been applied extensively to medicolegal examinations. This type of application has been useful in resolving claims of parentage in estate, immigration problems, mixed babies in hospitals, in cases of kidnapped children when kidnapper claims the baby as her own. Greatest numbers of cases involve disputed paternity.

A child cannot possess a red cell antigen unless it is present in one or both of his parents. The mathematical chances of proving exclusion have been calculated and the chances for exclusion increase as more blood systems are used.

DEMONSTRATION OF BLOOD GROUP SUBSTANCES³³

All blood-grouping tests are dependent on an observable reaction between a blood group substance and an antibody to this substance in serum. The type of antigen-antibody reaction used most commonly in blood group determination is agglutination, which results in clumping of red blood cells if the test is positive. Precipitation reactions are seldom used routinely, but are of value in forensic cases in differentiation between human blood and that of other species. The sera used for these reactions are produced by injecting human red cells in animals or human volunteers.

Agglutination or Hemagglutination Test

This test consists of demonstrating the agglutination of red cells after the cells have been mixed with appropriate antiserum in normal saline. Antibodies producing this change are called complete antibodies and represent immunoglobulins of the IgM class. The incomplete antibodies coat the cells but will not produce agglutination. These are of the IgG class of immunoglobulins and agglutination with these antibodies is produced by manipulating the system. In forensic cases, fresh

blood may not be available. Since, the agglutination test described above cannot be used on dried blood stains, secretions or tissues, one of several modifications of the antigen-antibody reaction must be substituted. The two often used methods are agglutination-inhibition and mixed cell agglutination tests:

Agglutination-Inhibition Test

This test consists of demonstrating inhibition of agglutination between red blood cells with a known antigen and antisera to this antigen. Extracts of dried blood, tissues and saliva can be used in this manner for testing, but relatively large amounts of materials are needed for this test.

Mixed Cell Agglutination

This requires smaller amounts of materials since it does not depend on preparation of tissue extracts. Dried red blood cells or other tissue cells are treated with a known antiserum. If the cells tested have antigens that react with antiserum, antibody will bind to cells. The reaction can be further adapted to test materials that have been soaked with human blood or secretions, e.g.: fibers stained with dry saliva from a group A individual and treated with anti-A antiserum will show adherence of group A blood cells that can be visualized under the microscope.

DETERMINATION OF BLOOD GROUP SUBSTANCES IN SECRETIONS AND TISSUES³³

Identification of blood substances in secretions and tissues found at the scene of a crime is more complex than it is with blood. Even in the fresh state, the only antigens that can be identified are A, B and H and these require more complicated techniques. The examination of secretions and tissues may be useful in corroborating findings from blood samples and may be particularly valuable in the absence of blood.

BLOOD GROUP SUBSTANCES IN SALIVA

The use of saliva in forensic science is based on the presence in the saliva of secretors of ABH blood group substances in fairly high concentration. All secretors show some H activity in their saliva, but larger amounts are usually present in the saliva of group O individuals than in those possessing A and B substances. Since saliva may be found on various objects at the scene of a crime, care must be taken that this evidence is not neglected or handled improperly.

In cases of human bites, saliva should be collected before making impressions. Swabs should be taken from different areas of the bite with clear records kept as to where the swabs were taken in relationship to the individual tooth marks. Since the victim's blood or tissue may be mixed with the attacker's saliva,

the interpretation of the tests requires accurate notation as to the degree of contamination. Take swab from normal adjacent site on victim's skin that would not have been exposed to saliva to serve as control for the blood grouping tests. Saliva should be collected in the same manner from floor, ground, or on various objects that cannot be moved from the site of crime. Since, ABH substances are widely distributed in nature, as part of the plant or animal world, the saliva sample may give a false-positive test due to contamination from the substrate. Similarly, the substrate may also contain inhibitors that interfere with the test for blood substances and thus be responsible for a false-negative test.

DENTAL TISSUES AND THEIR ROLE IN FORENSIC SCIENCE

TEETH AND THE BLACK DEATH

Teeth have been used to answer historical questions as well as identify victims.

For years, scientists and historians have sought to discover if the bubonic plague outbreaks during the Middle Ages were actually caused by the *Yersinia pestis* bacteria. Pulp was extracted from the teeth of people who had allegedly died of the plague, and the DNA tested for the presence of *Y. pestis*. Although it was found in some of the teeth, not all of the alleged plague victims' teeth contained the bacteria. Some of these people died of other diseases and not bubonic plague after all.

TYPES OF TEETH

- When teeth grow in, or erupt, they do so differently in each person.
- Teeth grow an average of four micrometers per day, so it is possible to give a rough age estimate based on teeth.
- It can also be possible to distinguish ethnicity from the teeth. Some Asians and Native Americans have incisors with scooped-out backs.
- The patterns of tooth wear also vary and can change over time. Not only can people be identified by their teeth, you can also learn a lot about their lifestyles and habits by the state of their teeth.

TOOTH IDENTIFICATION

Tooth enamel is harder than any other substance in the human body, which is why teeth remain long after all other parts have decayed.

- There is no database of teeth that corresponds with databases of fingerprints, so dental records are how forensic dentists identify the dead.
- Victims of fires are often identified by their teeth, which can withstand temperatures of more than 2,000 degrees Fahrenheit (1,093 degrees Celsius).

- Teeth that have been through especially intense heat are very fragile and may shrink, but they can be preserved with lacquer and used for identification as long as they are handled very carefully.
- Dental work, such as a partial or full coverage gold crown, will be distorted by fire but can still aid in identification.
- To identify a person from his or her teeth, a forensic dentist must have a dental record or records from the deceased person's dentist.
- Even if only a few teeth are available, a forensic dentist can still make a positive identification. The best comparisons come from X-rays.
- In addition to the dental records, forensic investigators can retrieve DNA samples by extracting the pulp from the center of the tooth.
- Unlike the enamel, pulp can be damaged by fire and other conditions, but it can also last for hundreds of years.
- Dental erosion will show as enamel being lost on the palatal surfaces which could be caused by a number of different conditions such as anorexia, chronic alcoholism and gastric problems. Each causes repeated vomiting, which causes acid erosion of the teeth.
- Staining visible on teeth could be due to fluorosis or tetracycline administration during tooth development or a number of causes resulting in intrinsic or extrinsic stains.
- Children who hold pencils or pins between their teeth may have wear facets on incisors.
- Dental identification is often the last resort, but it isn't always possible—some people simply can't be identified.

BITE-MARK ANALYSIS

Bite-mark analysis is extremely complex, with many factors involved in a forensic dentist's ability to determine the identity of the perpetrator.

The movement of a person's jaw and tongue when he or she bites contributes to the type of mark that is left.

Depending on the location of the bite, it is not typical to find bite marks where both the upper and lower teeth leave clear impressions—usually one or the other is more visible.

If the victim is moving while being bitten, the bite would look different from that inflicted on a still victim.

Bite marks are tricky because they're about more than just the teeth. Time can affect bite marks, and so can movement and pressure.

Forensic dentists use several different terms to describe the type of bite mark:

- Abrasion—A scrape on the skin
- Artifact—When a piece of the body, such as an ear lobe, is removed through biting
- Avulsion—A bite resulting in the removal of skin

- Contusion—A bruise
- Hemorrhage—A profusely bleeding bite
- Incision—A clean, neat wound
- Laceration—A puncture wound.

Several different types of impressions that can be left by teeth, depending on the pressure applied by the biter can be identified:

- Clear impression means that there was significant pressure
- Obvious bite signifies medium pressure
- Noticeable impression means that the biter used violent pressure to bite down.

BITE-MARK ANALYSIS CONTROVERSY

Forensic dentists may be giving juries the impression that bite marks are as unique as fingerprints or DNA but they are not as unique. Bite marks cannot be used as the only thing linking the suspect to the crime.

BOLD

BOLD is a forensic odontology laboratory at the University of British Columbia. It is the first and only laboratory in North America that is dedicated to full-time forensic dentistry research, casework and graduate teaching.

It is the place where laboratory discoveries and modern forensic methods are applied to dental evidence to assist in the resolution of legal issues.

BOLD is a center of excellence that aims to act as a resource for odontologists and other forensic scientists who deal with teeth, bones, saliva, DNA and dental records.

Experts here can provide assistance with:

- Investigation
- Identification
- Analysis
- Testimony.

CHILD ABUSE

Selwyn et al 1985, have defined child abuse as a non-accidental physical injury, minimal or fatal, inflicted upon children by persons caring for them.

"The battered child syndrome" is a term, which was introduced by Kempe in 1962. He pointed out that guilty parents were not confined to one socioeconomic class, and that whilst the syndrome might occur at any age, in general affected children were under the age of three years.³⁴

Reasons for reluctance to acknowledge child abuse by dentist:³⁵

- Lack of adequate histories.
- Lack of knowledge about the problem of child abuse and their role and responsibilities in reporting it.

- Concern about the effects on their practices if they report cases.
- Fear of confronting the parents.
- Lack of literature about dentists' experiences with cases of child abuse.

INCIDENCE OF OROFACIAL LESIONS

Cameron et al found that facial trauma is commonly found in children. **Becker et al** found that orofacial trauma in 49 percent of 260 documented cases was child abuse. Analysis of types of injuries that dentists may see showed that 33 percent were head injuries, 61 percent were facial injuries and 6 percent were intraoral injuries.^{34,35}

DETECTING CHILD ABUSE IN THE DENTAL OFFICE³⁶

When a child presents for examination, particularly if there is an injury involved, the history may alert the dental team to the possibility of child abuse.

The possibility of child abuse or neglect should be considered whenever history reveals the following:

- The present injury is one of a series of injuries that the child has experienced.
- The family offers an explanation that is not compatible with the nature of the injury.
- There has been an extraordinary delay in seeking care for injury.
- The family does not want to discuss the circumstances of injury.

TYPES OF CHILD ABUSE³⁷

Physical abuse	31.8%
Educational abuse	26.3%
Emotional abuse	23.3%
Sexual abuse	6.8%
Failure to thrive	4.0%
Intentional drugging or poisoning	not specified
Munchausen syndrome by proxy	not specified

CHILD NEGLECT³⁷

Child neglect can be defined as an act of omission or the failure to provide food, shelter, clothing, health care, safety need, dental care and supervision.

Types of Child Neglect

Emotional neglect	27.8%
Health care neglect including dental neglect	8.7%
Physical neglect	7.8%

EXAMINATION OF ABUSED AND NEGLECTED CHILD

Common points to be observed and examined:

1. Frozen watchfulness—Staring constantly. There are no spontaneous smiles and almost no eye contact.
2. Lack of cleanliness and indications of malnutrition.
3. Overdressed/underdressed children.
4. Fractured anterior teeth or torn frenum.
5. Multiple injuries in various stages of healing.

DEFINITIVE EXAMINATION FOR CHILD ABUSE/NEGLECT

- It requires a keen observation and detailed documentation when suspicion exists. A systematic approach should be followed and to protect the examiner legally, the dental assistant should be present in the room and aware of the dentist's suspicion, to verify and record the findings.
- Detailed examination and palpation of the skull looking for subgaleal hematomas and cephalatomas.
- Positive sign of any battle like laceration, scar, and bruise.
- Body surfaces that are covered should be examined by lifting up the clothes to the limit they allow.

PARENT CONSULTATION

Once the suspicion is confirmed, the parent should be informed that an injury has been noticed.

The explanation of the cause of the injury should be understood fully by the dentist. Any inconsistencies in the narration or change in attitude of the parent or lack of correlation between the injury and its cause should be duly noted down. Explanation of the cause of injury should be obtained from both the parent and child to reveal any discrepancies.

COLOR CHANGES OF BRUISES

0–2 days	Swollen, tender.
0–5 days	Red, blue, purple.
5–7 days	Green.
7–10 days	Yellow.
10–14 days	Brown.
2–4 weeks	Cleared.

OVERDIAGNOSIS OF CHILD ABUSE³⁶

While the importance of reporting suspected cases of child abuse and neglect cannot be overemphasized, the thoughtful practitioner should also consider the other side of the coin. **Kaplan** reviewed 15 cases that were misdiagnosed as child abuse. They included a child whose generalized bruises were later found to be related to cystic fibrosis. **McClain et al** reported on another supposedly abused child who was found

to have acute lymphoblastic leukemia of childhood. Kaplan concluded that overdiagnosing the battered child syndrome can be as harmful as failing to consider it.

Human Hand Marks

- Grab marks or finger-tip bruises: Oval shaped bruises that resemble finger tips.
- Linear grab marks: Pressure of entire finger when capillaries at the edge of the injury are stretched enough to rupture.
- Slap marks: Two to three parallel linear bruises at a finger width.
- Crescent shaped bruises: Due to pinching.

Strap Marks

- These are one to two inches wide, sharp border rectangular bruises of various lengths.
- Often lash marks are narrow, straight edged bruises or scratches caused by a thrashing with a tree branch.
- Loop marks are due to rope commonly breaking the skin and loop shaped scars because of force of the distal end.

Bizarre Marks

- Bizarre-shaped bruises with borders are nearly always inflicted when a blunt instrument is used resulting in a welt or a bruise (Fig. 15.8).
- The wide assortment of instruments used to abuse children suggests that the caretaker who loses temper, grabs whatever objects are handy.
- Circumferential tie marks on ankle or wrist can be caused when the child is restrained.
- Circumferential cuts are due to a narrow rope or cord.



FIGURE 15.8: Bizarre shaped marks on the back of a child indicative of physical child abuse

- A frictional burn or rope burn will result due to a piece or strap of sheeting used to restrain the child, presenting a large blister that encircles the extremity.
- Gagged abrasion is due to restraining of mouth to stop crying or yelling of children.

Facial Injuries Include (in order of decreasing frequency)

- Contusions and ecchymosis
- Abrasions and laceration
- Burns
- Bone fractures
- Bite marks.

Injuries of Dentition Include

- Traumatized or avulsed teeth indicating blunt trauma or pattern injury from instruments.
- Tears of the labial or lingual frenula.
- Oral mucosa torn from gingiva.
- Loosened or fractured teeth.
- Root fractures.
- Darkened/discolored and/or nonvital teeth indicating repeated trauma.
- Previously missing teeth.
- Trauma to the lip.
- Trauma to the tongue.
- Other soft tissue injuries.
- Fractures of jaws and associated structures.
- General neglect of the mouth.

BITE MARKS

The first man on earth “Adam” committed the sin of biting an apple and was punished by God. Despite this fact, man on earth did not realize the importance of bite marks and its proper utilization until late.

As no two fingers are identical, neither two mouths nor two teeth are exactly identical.³⁸

Biting is considered to be a primitive type of assault and results when teeth are employed as a weapon in an act of dominance or desperation.

Bite mark may be defined as a mark caused by teeth alone or in combination with other oral parts or as consisting of teeth marks produced by the antagonist teeth, which can present as two opposing arch marks.

MacDonald (1974) has defined a bite mark as a mark caused by the teeth either alone or in combination with other mouth parts.³⁹

Other definitions of bite mark are:

- “A pattern left in an object or tissue by the dental structures of an animal or human”.⁴⁰
 - “A bite mark may be defined as a pattern produced by human or animal dentitions and associated structures in any substance capable of being marked by those means”.⁴¹
 - “A bite mark is the registration of tooth cutting edges on a substance caused by jaw closure”.⁴²
 - “A bite mark is a mark made by the teeth either alone or in combination with other mouth parts”.
 - As has been discussed in a previous section, bite marks are produced in flesh, foodstuffs or a number of other materials by teeth and the surrounding soft tissue.
 - Marks in human body are often contributed by pressure from lips and tongue and from teeth themselves.
 - Dental evidence has become increasingly important in the investigation of non-accidental injuries to children.
 - The most common areas to be bitten in children are: head, neck, limbs and trunk.
- In female: Breast, arms and legs.
In males: Arms and shoulders.

CLASSIFICATION OF BITE MARKS

Depending on biting agent

Human:

- Children
- Adults

Animals:

- Mammals
- Reptiles
- Fish

Mechanical:

- Full denture
- Saw blade tooth marks
- Bicycle chain and others like electric cord.

Depending on material bitten

Skin:

- Human
- Animal

Perishable items:

- Food items like cheese, apple.

Non Perishable

- Unanimated objects such as pipes, pens, pencils.

Depending on degree of biting

Definitive bite marks: Tooth pressure marks are formed when a direct application of pressure by the biting edges has caused tissue damage.

Amorous bite marks: These marks are made slowly with absence of movement between teeth and tissues. Lower teeth marks are formed when teeth are pressed into tissue with gradually increasing pressure. Marks of upper teeth form a

series of arches where the tissues are sucked into the mouth and pressed against the back of the teeth with the tongue.

Aggressive bite marks: These marks show evidence of scraping, tearing and avulsion of tissues. Usually involves ears, nose, or nipples. Such bites may be difficult to interpret.

WEBSTER'S CLASSIFICATION⁴³

It is not uncommon to note bite marks in foodstuffs, especially in cases of theft or robbery, where the involved may conveniently grab a bite from the kitchen refrigerator or a supermarket food shelf.

Type I: Food item readily fractures with limited depth of tooth penetration, e.g. hard chocolate.

Type II: Fracture of fragment of food item with considerable penetration of teeth, e.g. bite marks in apples and other firm fruits.

Type III: Complete or near complete penetration of food item with slide marks, e.g. cheese.

MECHANISM OF BITE MARKS

Tooth Pressure

- Marks caused by a direct application of incisal edges of anterior teeth or occlusal surfaces of posterior teeth.
- Marks depend on force applied and duration of force.
- A pale area represents incisal edges and bruising represents margin of incisal edge.
- Shape of marks may be useful in the identification of specific tooth.
- Tooth mark pattern as an attack or defensive bite mark.

Tongue Pressure

It is caused when material is taken into the mouth and pressed by tongue against the teeth or palatal rugae.

Bite marks of sadistic origin exhibit a central ecchymotic area or a suck mark with a radiating linear abrasion pattern surrounding the central area and resembling a sunburst.

Tooth Scrape

- Caused by teeth scraping across the surface of the skin.
- These marks are usually inflicted by anterior teeth.
- May appear as scratches or abrasions.

FACTORS AFFECTING BITE MARK INJURIES

1. Inherent skin factor.
2. Age.
3. Sex.
4. Time.
5. Vascularity.

CHARACTERISTICS OF HUMAN BITE MARKS FOR IDENTIFICATION

Human bite marks include an elliptical or ovoid pattern containing tooth and arch marks.

An arch mark may indicate the presence of four to five teeth marks reflecting the shape of their incisal or occlusal surfaces.

Other significant findings may include:

- Presence or absence of any tooth
- Peculiar shape of any tooth
- Mesiodistal dimensions
- Arch form and size
- Relationship between upper and lower jaws
- Any rotation, fractured teeth, microdontia, diastema, etc.

BITE MARK ANALYSIS

Description of the bite mark:

Demographics

- Name of victim
- Case number
- Date of examination
- Referring agency
- Person to contact
- Age of victim
- Race of victim
- Sex of victim
- Name of examiner(s).

Location of bite mark

- Anatomical location
- Surface contour: Flat, curved or irregular
- Tissue characteristics:
 - a. Underlying structure—bone, cartilage, muscle, fat.
 - b. Skin—relatively fixed or mobile.

Shape

Round, ovoid, crescent or irregular.

Color

The color should be noted, e.g. red, purple, etc.

Size

Vertical and horizontal dimensions of the bite marks, preferably in metric system.

Type of injury

- Petechial hemorrhage
- Contusion (ecchymosis)
- Abrasion
- Laceration
- Incision
- Avulsion
- Artifact.

COLLECTION OF EVIDENCE FROM VICTIM

1. Photography
2. Salivary swabbing

3. Impressions
4. Tissue sample.

Photography (Fig. 15.9)

Obtain or produce photographs which meet the following guidelines:

- Orientation and close-up photographs should be taken.
- Photographic resolution should be of high quality.
- Both color and black and white photographs should be taken.
- If color film is used, accuracy of color balance should be assured.
- It is recommended to start with the broader orientation photographs then move towards close-up photographs, which are used in detailed documentation of the injuries themselves.
- Photographs of the mark should be taken with and without a scale in place.
- When the scale is used, it should be on the same plane and adjacent to the bite mark. It presently appears desirable to include a circular reference in addition to a linear scale.
- The American Board of Forensic Odontology (ABFO) no. 2 scale is widely used and recommended, but many other scales can be used, including rulers, coins or any other objects that can be used as a size reference when the photographs are enlarged to life size. Such scales or reference items become part of the evidence and should be maintained with rest of the case evidence.⁴⁴
- The most critical photographs should be taken in a manner that will eliminate distortion.
- In the case of a living victim, it may be beneficial to obtain serial photographs of the bite mark.



FIGURE 15.9: Bite marks on thigh of a child

- Good quality extraoral photographs—both full face and profile.
- Intraoral—frontal view, two lateral views, occlusal view of each arch and any additional photograph that may provide useful information.
- Maximum interincisal opening with scale in place.
- If inanimate materials, such as food stuffs, are used for test bites, the results should be preserved photographically.
- The camera lens should be positioned at 90° to the surface of the skin that bears the wound. Several exposures should be made at varying magnifications.
- The position of light source should be varied to illuminate the wound from multiple angles and to be certain that highlights of any surface irregularities are documented in relief.
- All photographs must bear a legend containing the necessary identifying information.
- At least one photograph of the entire injured area should be taken with no scale in place to show that no injuries were purposefully obscured by the scale.^{38,45}
- Additional visible light technique used to photo-document bite mark injuries is referred to as alternative light imaging or visible light fluorescent photography. This technique is used in specialized situations.
- Digital photography has many technologic improvements for visible light documentation of bite mark injuries. Digital camera captures image on a charge-coupled device (CCD) that can be transferred to a computer for processing and printing. One advantage of this is that the image can be changed to black and white, eliminating the step of taking separate black and white photographs, as must be done with film.
- In addition to visible light photographic documentation, nonvisible light can be used to record bite mark injury. Shorter-wavelength UV light and longer wavelength infrared (IR) light can be used. These techniques present the forensic dentist with another means to document and preserve details of bite mark injury.
- Epiluminescence microscopy is a dermatologic technique developed for evaluation of pigmented skin lesions. The application to bite mark analysis was discussed at the AAFS meeting in 1999. This technique, through rendering the stratum corneum translucent, can aid in visualization and photographic documentation of bite marks.⁴⁶
- Wearing gloves is strongly recommended during swabbing because that prevents contamination of evidence. We each secrete the ABH blood groups in saliva, seminal fluid, tears and perspiration. In 80 to 85% of most individuals, the levels are high enough for routine testing to be effective.⁴¹
- Swabbings of bite injury are done to recover trace evidence. It is recommended that such evidence be collected whenever possible because it is not possible to inflict a bite injury without leaving biologic trace evidence. Harvey estimated that 0.3 ml of saliva is deposited when making a bite mark. Ideally, the site should not be washed or contaminated by improper handling. Saliva swabbings or washings can be performed using a single cotton swab technique for recovering salivary amylase. If amylase is present in sample, ABO/ABH blood group classification is undertaken. Another unbitten site must be swabbed for a control sample.
- Swabbings are done to collect DNA present in salivary trace evidence. The double swab technique involves moistening the site with a swab moistened with sterile saline, then removing moisture with a second dry swab. Both swabs are sent for analysis. Research has shown recovery of biter's exfoliated epithelial cells from salivary trace evidence. The cells can provide DNA for analysis.⁴⁶

Impressions (Fig. 15.10)

- Whenever required, make impressions of the bite mark.
- Use ADA specification impression materials and make note of it in report.
- Support should be provided for the impression material to accurately reproduce body contour.
- Material used to produce cast should produce accurate details in impression.
- Master casts should be prepared using ADA specified Type IV stone.
- Additional models when required, should be duplicated from master casts using accepted duplication procedures.
- Teeth and adjacent soft tissue areas of master cast should not be altered by carving, trimming, marking or other alterations.
- One of the better impression materials to use is a vinyl polysiloxane (VPS) or similar low to medium viscosity material. VPS and polyethers or polysulfide impression materials have been found experimentally to be extremely accurate.^{47,48} The use of stiffer mixtures, such as heavy body or more firm type materials should be avoided as these distort the injured area due to pressure used to apply the materials.
- Alginate impressions usually are enough and packs of powder, measuring cylinders, rubber bowls and spatulae with full and part mouth trays, disposable syringes, etc. are required.

Salivary Swabbing

- After photographs are taken, salivary swabs should be done.
- Whenever possible, salivary trace evidence should be collected according to recommendations of the testing laboratory.

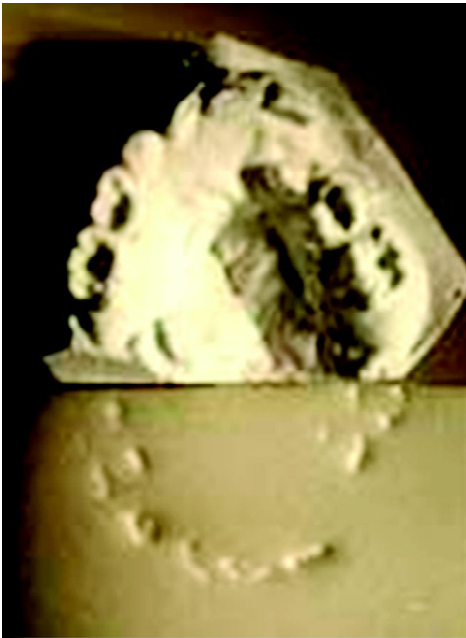


FIGURE 15.10: Making impressions of bite marks and assembling casts for identification

- **Technique:** Use the premixed materials in syringe with a small orifice tip; they are injected directly onto the injured site. Small tips used on the conventional impression syringes by dentists work very well. Material is injected slowly so that it flows into lower areas of the mark and does not trap air that will create a bubble or void in finished negative impression.
- VPS materials are flexible when done in a thin sheet as would be used in a bite mark impression. So, the material should be supported and reinforced by dental laboratory stone, acrylic dental impression tray material, thermoplastic dental tray or fracture material and an orthopedic thermoplastic mesh material (Hexcelite).
- To ensure a mechanical locking of stone and impression material, staples are dipped into extra impression material and placed on end in impression material on injury site.

Tissue Samples

- In some instances, it may be necessary to excise the bite mark from a deceased victim to facilitate the preservation of the evidence as well as to aid investigations relating a possible biter to the injury.
- The bite mark and adjacent tissues are attached to a rigid ring of plastic before excising to preserve orientation of injured tissue.
- Plastic material used to stabilize tissue usually is cold-cure acrylic or any thermoplastic material. The tissue is attached

to the ring with cyanoacrylate adhesive, sutured to ring and excised.

- The excised tissue is preserved in a tissue fixative, placed in a sealed plastic bag and stored.
- The excised tissue can be transilluminated by shining a light from the dermal side or inner aspect of tissue. Successful transillumination studies can provide additional evidence for use in bite mark analysis.⁴⁶

COLLECTION OF EVIDENCE FROM SUSPECT

- Before collecting evidence from suspect, the dentist should ascertain that the necessary search warrant, court order or legal consent has been obtained and should make a copy of this document as part of his/her records.
- At least two sets of dental casts should be fabricated. All necessary information should be noted on the base of each cast and a virgin set should be placed aside for safe-keeping.⁴⁶
- **Test Bites or Sample Bites:** It is useful to collect sample or test bites of victim and suspect. Sample bites usually are made in wax medium, such as Aluwax, pink baseplate wax or Coprwx. Wax is bitten or indented with incisal edges of teeth because bite mark analysis involves position, shape and alignment of incisal edges of biter's teeth as they relate to injury, care must be exercised to avoid biting all the way through the wax.
- Styrofoam has been used as a test bite medium for the demonstration of the pattern of the incisal edges of teeth.
- Test bites can be done with the stone models of the biter's teeth into the skin of a volunteer.⁴⁶

Recent Advances for Collecting Evidences

1. Xeroradiography
2. Transillumination
3. Videotape analysis
4. Superimposition technique
5. Scanning microscopy
6. DNA fingerprinting.

ANALYSIS OF BITE MARKS

Distortion arises from three factors:

1. Inherent distortion within the mark itself due to the mechanics of biting and physical and biological properties of skin and underlying structures.
2. Distortion produced by trying to represent a three-dimensional mark on a two-dimensional photograph.
3. Distortion produced in printing the negative to a life-size or preset magnification.⁴⁹

COMPARISON TECHNIQUES

Once all relevant data are assembled, comparison of the mark with the suspect's dentition can begin. Comparison involves not only use of superimposition techniques but also, the collection of all evidence, including physical features as well as dynamics of the bite and the compatibility of the features with suspect's teeth.

Life-size Comparisons

Direct method: The models can be placed directly over the photographs and corresponding points can be demonstrated, e.g. fit of the incisal edges. Advantage of this method is that models can be moved to demonstrate the dynamics of the bite by showing slippage and scraping.

West and Friar, 1989, used direct model-to-victim comparisons to demonstrate marks caused by slippage of teeth, by placing the models directly over the breast of a deceased victim and dragging the model across the skin to demonstrate how marks were produced *in vivo*. The entire procedure was photographed, videotaped and produced as evidence.

Furness, 1968, described a method similar to that used by fingerprint officers, where lines are used linking various points of correspondence between models and teeth. Advantage of this technique is that fine detail such as cervical margin indentations can be seen and compared. Disadvantage is that the technique cannot be used on grossly distorted marks.⁴⁹

Indirect methods⁴⁹: Indirect comparisons are made using transparent overlays on which biting surfaces of the teeth are recorded; these are placed directly over the marks on the photograph. This method was first used by **Sorup, 1924**, and cited by **Strom, 1963**. **Morgen, 1943**, used photographs of models to produce overlays. The photographic production of overlays by various methods is the most reliable way of producing true reproductions of dentitions.

Use of photographic tracings (reverse negatives) can be enhanced by using oblique lighting on model to highlight specific features. This model can be photographed with a scale at the occlusal surface and reverse negative produced, which shows not only biting surfaces but other anatomical details as well.

Other methods such as pressing the teeth into wax and photographing the indentations can produce accurate overlays. The indentations can be enhanced if sprinkled with radiopaque powder and radiographed. **Farrell et al 1987**, used computed axial tomography (CAT) scanning to produce overlays of dentition at varying depths, so that teeth not involved initially in the bite were shown at precise depth at which they began to be involved in the mark.⁵⁰

Assisted Comparisons

It should be noted that these methods are best used as confirmation of the result rather than as the sole assessment.

- **Tsutsumi and Furukawa, 1984**, described the use of a measuring instrument called Vectron which is similar to a dental surveyor and measures distances between fixed points, angles and radii.
- **Bang, 1976**, used stereometric graphic analysis in mark investigation and produced a contour map of the features of the mark and suspect dentition. A visual representation is then available which is compared electronically with the mark in terms of longitudinal contours and topographical features.
- Light, electron and split-image microscopes can be used. **Bang, 1976**, and **David, 1986**, both described the use of the scanning electron microscope to good effect. Ligthelm et al 1987, have added the reflex microscope to the range of microscopes in use. Various electronic techniques such as splitting the image, image stacking, bite edge enhancement, etc. can be used.⁴⁹
- Quantitative forensic evaluation of bite marks with the aid of a shape analysis computer program ("SCIP"—Shape Comparison Interactive Program) has been employed to quantify the comparison in the form of Similarity Index (SI) between offenders teeth and the bite marks produced on a standard flat wax form.^{51,52}
- Xeroradiography and transillumination, as described by **Rawson et al and Dorion, 1987**, respectively, are specialized techniques that have been used in bite mark analysis. Both these techniques require removal of bitten tissue. In Xeroradiography, a layer of iodine contrast material is used and radiographs of the mark are taken. This is only applicable when indentations are present. Transillumination utilizes the changed hemorrhagic structure of the tissue which is viewed under a light source that enhances the areas of varying hemorrhagic density. This is a useful technique when the mark is very diffuse.
- Biopsy and histological examination of bite marks is confined to the deceased. Whittaker, 1989, refers to methods of staining for iron, other blood products, elastic fibers and collagen. He also established, using histology, whether mark was inflicted ante- or post-mortem. **Glass et al 1980**, used histology to demonstrate the presence of micro-organisms and calculus within the lesion, thereby confirming that the mark was caused by teeth.⁴⁹
- **Experimental marks:** The use of experimental marks to analyze a bite mark has been used as an aid to comparisons. They can be produced under varying circumstances. **Jakobsen and Keiser-Nielsen, 1981**, stipulated that three

criteria should be met before undertaking experimental bite marks:⁵³

1. The mark has been established as having been made by human teeth.
2. A reliable reproduction, e.g. a photograph, is available.
3. The circumstances under which the bite was inflicted are known.

Vale et al 1976, made a rubber model of the part that was bitten and produced similar marks using the suspect's dentition on the model.⁵⁴ Various attempts have been made to produce skin-like substance, such as baker's dough (*Buhtz and Erhardt, 1938*, cited by *Jakobsen and Keiser-Nielsen, 1981*)⁵³ or pigskin (*Whittaker, 1975*).⁵⁵

BITE MARKS IN INANIMATE OBJECTS

Inanimate objects in which tooth marks can be made fall into three broad categories:

1. Edible substances.
2. Objects that are habitually chewed.
3. Substances making contact with teeth in falls or skirmishes.

Whatever the substance, the overriding priority is preservation of the evidence.⁴⁹

Perishable Substances⁴⁹

1. Saliva swabbing.
2. Object should be examined for fingerprints.

Preservation of foodstuff is an urgent priority as all food deteriorates once exposed to air. This is done by placing the substance in an airtight bag in a refrigerator or immersing in a medium of 5 percent glacial acetic acid, 40 percent formaldehyde solution and 70 percent ethanol in the ratio of 5:5:90 (FAA solution which has preserved apples for 10 years).

Non-Perishable Substances

Non-perishable objects are dimensionally stable and may reproduce marks. These objects are bullet, pipe stems, pencils and soap.⁵⁶

Long-term preservation can be made by photography and model preparation. *Stoddart*⁵⁷ described a method for making models of perishable substances. For other inanimate objects, modern two-stage crown and bridge impression materials give satisfactory results. Models can be made using plaster, acrylic or composite restorative materials.

HABITUAL CHEWING MARKS⁴⁹

These are usually found on pipe stems, pencils and key bows. Often cusp marks are present. Cusp marks made by human canines, premolars and molars can be similar to those produced by dentition of dogs and cats.

A suggested method for analyzing multiple cusp marks is as follows:

- Isolate and identify the shapes of marks, i.e. triangular (canines and premolars), rectangular (incisors) or round (molar cusps).
- Look for multiple involvement of same cusp.
- Check for corresponding upper and lower tooth cusp marks.
- Check for the orientation of the object in the mouth.
- Enlarge photographs of cusp marks to two or three times life-size.

Histopathologic and clinical changes used to monitor the time elapsed (aging) in skin injuries associated with bite marks:²⁴

- At 4–8 hours – PMNs (polymorphonuclear leucocytes) with peripheral front predominate. Clinical color is red-blue-purple.
- At 12 hours – PMNs predominate
- At 16–24 hours – Macrophages peak
- At 24–36 hours – PMNs peak and peripheral fibroblasts are seen
- At 1–3 days – Central necrosis is seen
- At 3+ days – Hemosiderin pigment is seen. Clinical color of the bite mark is green-blue.
- At 4 days – Collagen fibres predominate
- At 4–5 days – Capillary growth predominates. Clinical color of the bite mark is brown-yellow-green
- At 6 days – Lymphocytes peak at periphery
- At 10–14 days – Granulation tissue predominates. Clinical color of the bite mark is tan-yellow.

FORENSIC ANTHROPOLOGY (FIG. 15.11)

Forensic odontologists often work with specialists in other fields of forensic science. Besides the forensic pathologist, the forensic anthropologist is perhaps the next most common collaborating colleague. Forensic anthropology was not widely practiced on a regular basis until after World War-II. The last 20 years have seen rapid growth of this field in developed countries.

Forensic odontologists and anthropologists are both primarily interested in the hard tissues of the body. The forensic anthropologist usually gives more attention to the osseous material rather than dental evidence. This does not mean that the anthropologist does not study the evolution and variation of human dentition nor does it imply that the dentist is unaware of the anatomy of the skull.

ROLE OF FORENSIC ANTHROPOLOGIST

Forensic anthropologists may be asked to give very specific information such as an estimation of age at death or they may be asked to give all information that can be determined from skeletal remains.



FIGURE 15.11: The Department of Anthropology at the US National Museum in 1904

When remains of deceased cannot be fully evaluated during a normal postmortem examination by the pathologist, a forensic anthropologist is called for. These remains become unidentified due to partial or complete decomposition of soft tissues, burned or mutilated by intent or accident.

In cases where the body is intact, the specialist in human osteology may be helpful in determining weapon characteristics from damage caused to the skeletal system.

The anthropologist may be able to establish identification by a number of means, including comparison of antemortem and postmortem radiographs. The anthropologist must remove remaining soft tissue from the skeletal evidence before any analysis can be done. In a mass disaster this is not always possible because of the time factor, so the technique should be modified or limited to those that can be used with soft tissue remaining. More radiography is necessary then.

Soft tissue removal is accomplished after radiography by boiling, preferably under an odor hood. Boiling of remains reduces the biohazard exposure for the staff of the anthropology laboratory as well as those handling the remains afterwards, such as forensic dentist, prosecutors and other attorneys.

FORENSIC LABORATORY EQUIPMENTS

Forensic anthropology laboratories that are properly equipped have odor hoods over stainless steel sinks, an X-ray machine, radiograph dry processing and duplicating equipment, osteometric instruments, video superimposition equipment and ample macrophotographic capabilities. Adequate space for layout and storage of skeletal remains must be available.⁵⁸

TECHNIQUES

Various techniques are used by the forensic anthropologist. It is wise to discuss only those techniques that are useful to the forensic dentist.

Remember, no single technique is always the best indicator of age, sex or race. Multiple indicators are the key—not single indicators or techniques.

First step is to confirm that whether remains are human and how many individuals are present. Incorrect conclusions at this point lead to embarrassment or worse.

AGE ESTIMATION FROM POINT OF VIEW OF ODONTOLOGIST AND ANTHROPOLOGIST

Dental aging techniques based on formation of crown, eruption and root tip completion are commonly used by dentists, but occasionally age estimates derived from dental information may be in conflict with skeletal age determinations.

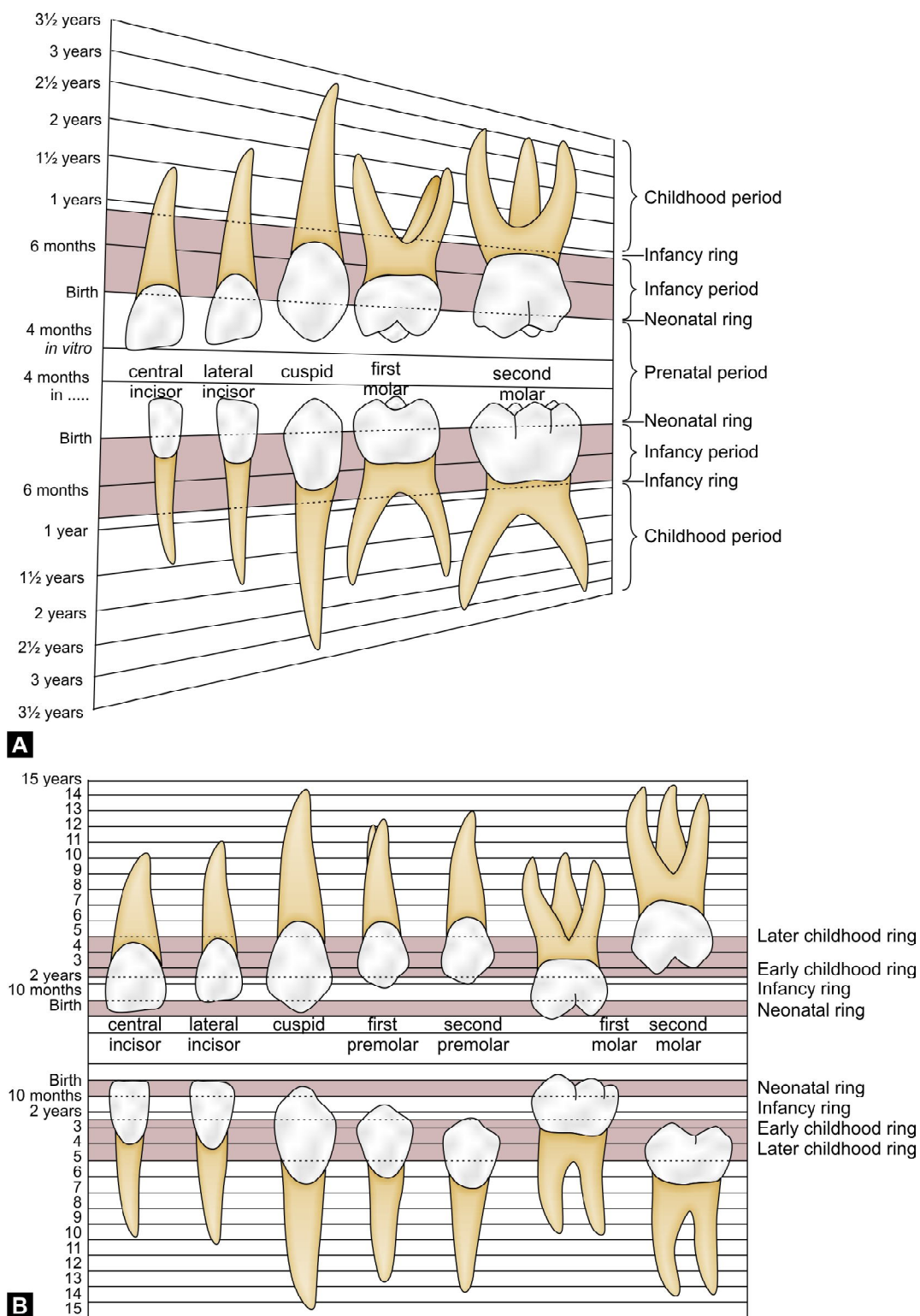
It is now common practice to derive age estimates using one's experience and judgment to arrive at the best estimate. There is no agreement of anthropological age estimate and the dental age estimate especially in remains of teenage victims.

Increased caution is indicated when very poor oral health is present. In cases of very poor oral health, such as in transient people, dental age may appear to be greater than normal. Indeed, transients and migrant workers often show increased periarticular lipping in the joint and osteophytic lipping in the vertebrae.⁵⁸

DEVELOPMENT OF HUMAN DENTITION BY SCHOUR AND MASSLER

The surveys of *Schour and Massler, 1941*,⁵⁹ have their origin in the work of *Logan and Kronfield, 1933*,⁶⁰ and are often cited (Figs 15.12A and B). In 1935, *Schour and Massler* published a numerical development chart for the deciduous and permanent teeth. The 'Schour and Massler Development of the Human Dentition' chart is periodically updated and is published life-size by the American Dental Association. Its appeal is obvious: both developing dentitions are displayed *in situ*, and it includes root resorption sequences for the deciduous teeth. As the drawings are life-size, it is easy to make direct comparisons with either radiographs or individually removed developing teeth. Criticisms are that the chart does not have separate surveys for males and females, and the range about the mean ages from 2 years to 15 years is put at 6 months and is thus too narrow.

Ciapparelli, 1985, compared the Schour and Massler data with a sample of schoolchildren.⁶¹ The mean ages from 4 years to 16 years corresponded well in the males, the females developing, on average 3 to 6 months earlier. The variation



FIGURES 15.12A and B: Developmental pattern of the child as reflected in the calcification pattern of teeth
A: Deciduous dentition, B: Permanent dentition. (Massler and Schour and Poncher)

was comparable in children 4 to 6 years old, but by the age of 12 years the male variation was double, and at 16 years treble, that of the Schour and Massler variation.

In spite of these shortcomings, these surveys do have a useful role to play in forensic investigations.

SEX DETERMINATION OF SKELETAL REMAINS

Most experienced forensic anthropologists of their time, Wilton Krogman, could determine the sex of skeletal remains correctly in about 80 percent of the cases when using the skull only, but about 90 percent correctly when the pelvis was also used.⁶² Forensic dentists consider only skulls or jaws for sex determination. The forensic anthropologist can usually bring greater precision to gender determination by using the entire skeleton remains.

COMPARATIVE FEATURES OF MALE AND FEMALE SKULL

The male skull is larger than the female skull, has better marked muscle attachment areas (nuchal and temporal lines); larger and blunter mastoid processes, more superciliary arch development, much blunter superior orbital margins, heavier zygomatic arches, larger jaws and more sloping foreheads.

Males may show everted or neutral gonial angles, while females usually show inverted or neutral gonial angles. The anterior mandible (chin) may be squared or rounded in males, but is usually pointed or rounded in females.^{58,63}

Determination of sex in prepubescent remains is very difficult. Puberty begins development of many secondary sexual characteristics. One usually does not count the female and male features in the immature skeleton to find which predominate. If such a skeleton shows any male features, it is probably male.

There is less gender variation in the age of dental development than there is in skeletal development. Males lag behind females in skeletal maturation.^{58,63}

RACE DETERMINATION (FIGS 15.13A TO C)

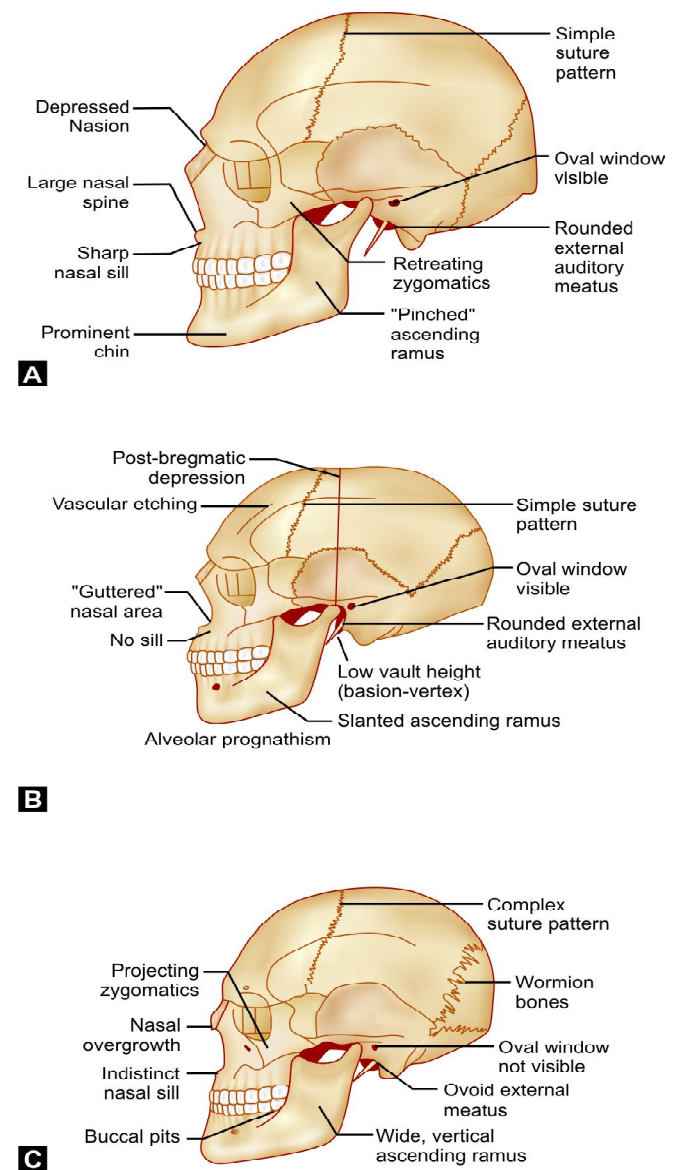
Race is a population concept. Races are "populations which differ in the frequency of some genes" (Dobzhansky, 1950).⁶⁴

Since individuals within that population vary considerably in their genes, it is very difficult to assign any individual to a particular race with any reliability. The racial identity that we carry with us throughout our lives is a sociological label, not a biological reality.

Obviously, there is considerable racial information in the teeth, but individual teeth are seldom diagnostic. Shovel-shaped maxillary incisors (trace, semi or full), for example are considered a Mongoloid trait and are found in 100 percent of Aleuts studied, but they may be found in individuals from any

racial group in the world. The fact that a forensic skeleton has shovel-shaped incisors may suggest the possibility of Asian origins, but does not exclude Eastern Europeans, Africans or even Polynesians. Similarly, large mesiodistal incisor diameters suggest African or Oceanian ancestry, but the range of variation in all races precludes any absolute conclusion.

The shape of the upper dental row (V-shaped in Whites, U-shaped in Blacks and horseshoe-shaped in Mongoloids), the width and shape of the nasal aperture, the development of the nasal spine and the shape of the lower margin of the nasal



FIGURES 15.13A to C: Race determination by skull bones: A: Caucasoid; B: Negroid; C: Mongoloid

aperture, orbital and supraorbital shapes, relative length and height of the braincase and the shape of the occipital bone are some of the cranial features that are useful in the identification of racial affinity. Alveolar prognathism, defined by anthropologists as the anterior projection of the jaws, is also a good trait for race determination.^{63,58}

HEIGHT DETERMINATION

Height can be estimated after age, gender and race of the remains are determined. For adults, the **Trotter and Gleser** (1952) formulae are probably the best. Separate formulae are used for each of six major long bones.⁶⁵ In case of the humerus, radius, ulna, femur and fibula, the measurement used is the maximum length. The maximum length, not the bicondylar length, of the femur is used. The tibia is measured from the most superior point on the lateral condyle to the most inferior point on the medial malleolus, parallel to the shaft of the bone. Always use the formula, which has lowest standard error of the estimate for the best estimate of stature.

After age, sex, race and height are determined, possible identifications are usually proposed by investigators assigned to the case. The identification must be proven biologically; by fingerprints, a good dental record showing multiple restorations or extractions, antemortem/postmortem radiograph comparisons, complex medical histories involving the skeleton or teeth or sometimes, by superimposition.

The investigators must secure all useful records on the deceased. Obviously, dental records and radiographs must be sought, but medical radiographs, medical records, DNA reference samples from appropriate relatives and photographs (especially “mug shots”) must be secured. If any ridge detail remains in soft tissue, fingerprints may still be useful. If hair is still present in the remains, reference samples may be obtained from the combs, hairbrushes or handbags of the missing person.

At some point during the analysis of the remains, trauma analysis is necessary. While skeletal damage may be obvious, sometimes skeletal evidence of perimortem injury is very subtle, such as fractures of the alveolar margins, chipped teeth, longitudinal enamel fractures or damage to the very thin cortex of articular bone, such as the mandibular condyles. The remains where skin is no longer intact should be radiographed prior to maceration to locate metal fragments from knife tips or debris from gunshot wounds. Lead debris may still be found on bones that have remained exposed to the surface environment for more than a decade.

If it becomes necessary to prove the metal debris located radiographically on bones is in fact lead, proton induced X-ray emission (PIXE) analysis may be used. Physics and Nuclear Departments at universities with an accelerator can do this nondestructive analysis.

Fragmented skulls and sometimes other bones must be reconstructed to visualize perforations from gunshot wounds. Fractures must be recorded by photographs and diagrams. Patterns of radiating fractures can demonstrate the type of weapon used, the site or sites of impact, and the number of wounds or the sequence of wounds. Bevelling on gunshot wounds will frequently show direction of the projectile.

Firearm caliber cannot be accurately determined from the wounds. Skulls fractured in blunt trauma may show patterns characteristic of the weapon (**Maples, 1986**).⁶⁶ Hammers, pry bars, jack handles, handgun butts and muzzles, beverage bottles, axe handles and many other common tools and weapons often leave very distinctive patterns. The damage or perforation is the result of the maximum cross section of the weapon that has passed through the surface of the bone.

Incised wounds (cuts or stabs) are commonly found on bones. Scalpels should not be used to open the body near any skin perforated by decomposition or wounds. During macerations, no metal instruments should be used that may damage the bone.

In examining bones for incised marks, every bone surface should be examined with magnification (X2 to X3 is ideal). Anterior surfaces of cervical vertebrae, inferior margins of the mandible, ribs, sternum, clavicles and posterior portions of thoracic and lumbar vertebrae should receive particularly careful attention. When bones are found disarticulated, it is important to place damaged bones back into articulated positions with adjacent bone when trauma is considered. If a stab wound severed a transverse process of a thoracic vertebra, one would expect damage to the rib at that location if injury occurred around the time of death with bones in their proper anatomical positions.

Dismemberment or decapitation will inevitably leave evidence on skeletal remains. The type of saw used for dismemberment is important. The grooves made from the saw teeth may travel in straight parallel lines (band or other power saw), straight but overlapping lines (hand saws), curved lines (oscillating or rotating circular blade) or the very coarse cuts of a chainsaw. Chainsaws may leave chainsaw oil on the bones and hacksaw blades may leave distinctively colored paint on the cut bone surfaces.

Bodies are cremated with various internal accretions such as prosthetic joints, surgical staples, vascular clips, surgical wire and wire catheters, dental prosthesis, orthopedic pins, nails, plates and screws. So before beginning analysis, the expert may separate the remains by particle size using proper analytic sieves.

The skeletal evidence is rich in information. The forensic anthropologist, working as part of a team of forensic pathologists, odontologists, and other forensic scientists, can greatly add to the results of the analysis. Indeed, the results of

the scientists working as a team and discussing the case at all stages of the investigation greatly exceed what each expert can do individually.⁵⁸

THE FETAL SKELETON (FIG. 15.14)

A few circumstances come to forensic odontologists when he has to work on a fetal skeleton, particularly calcified tooth caps of facial skeleton, so this topic is included here.

Calcified tooth caps can be retrieved from the whole fetus throughout the second and third trimesters of pregnancy. These tooth caps can be examined, identified and compared with standard charts or the whole dentition can be collected, dried to constant weight and from the mass of calcified tissue present and reference to appropriate charts, the age of the fetus can be estimated. This dental evidence that is often missing is firstly because the anatomists rarely wait for their specimens to putrefy before examination. Putrefaction is important because it liberates the tooth caps from the forming alveoli of the jaws. It is often assumed that the deciduous teeth remain safe in their crypts even after decay of the soft tissue; unfortunately, this is not so. Consequently, when fetus putrefies, the tooth caps fall from the jaws.⁶⁷

These fragments are small; for example, the calcified part of the first permanent molar is only about the size of a pinhead at birth and weighs about 1 mg. Such pieces can be easily be lost, to the soil or lost in investing materials such as clothing,

rag or even in the folds of plastic bags that have been used to wrap the corpse. Pieces may be identifiable and reconstruction may be possible, but a single cusp from the deciduous second molar can be extraordinarily difficult to distinguish from the single cusp of a deciduous canine.

In practice, dental evidence is unlikely to be complete enough for accurate age determination of the fetus for the following reasons:

- Tooth caps are small and fragile.
- They may be difficult (or impossible) to gather or identify.
- This problem is often made worse by poor scene-of-crime technique.

ASSESSMENT OF SKELETAL REMAINS⁶⁷

In the absence of teeth, what can be inferred or deduced from the bony part of the skeleton?

First thing is to identify whether the bones are of a human or not. If cranial bones are present, the answer is obvious. When the head is missing then it becomes more difficult. The bones of small animals (rat, rabbits) or large birds such as chickens are often mistaken by the ordinary person for fetal or neonatal human remains. It is worth remembering that bird bones have to be extremely light to be compatible with flight and therefore have large medullary cavities, whereas the bones of small mammals are usually mature and have completely fused epiphyses. Human bones of similar size really only comprise the diaphysis and therefore have no articular appendages.

All bones collected should be identified as far as possible, preferably by comparison with a reference collection of prepared skeleton of known sex and maturity. The bones should then be laid out in their approximate anatomical relationships on black card or filter paper together with a measuring scale. Particular care should be taken to assign a side or establish the handedness of bones, since to find two left zygomatic bones or clavicles even of the same size has obvious implications. If there is a body of a single fetus wrapped in a plastic bag and discovered later after putrefaction has destroyed the soft tissues all that may be necessary to put the contents of the bag through a sieve aided by copious quantities of water. The sieve mesh size should not be too fine or too coarse. It is better to use a medium sized domestic kitchen sieve.

If the soft tissues are intact, the bones can be examined in two ways. The first method is radiographically. If the object-film distance is no closer than one meter, the inevitable magnification inherent in all radiographic techniques is negligible and can be discounted when bone images are measured to determine bone size and hence fetal maturity. It is not always possible to lay all bones flat against the film. Articulated cranial bones are impossible to see individually



FIGURE 15.14: Fetal skeleton

without the superimposition of other structures. The dimensions of head also introduce an unacceptable degree of distortion into any radiographic images for accurate measurements to be made.

This leads to the second method of examination: the freeing of the bones from their investing soft tissues and their subsequent measurement directly using vernier calipers.

Determination of fetal age is made from estimates of fetal size. The parameter of size of the fetus that most closely correlates with gestational age is length measured from the crown of the head to the heel of the foot with the body laid out straight. The relationship is summarized by Haase's rule.⁶⁸ Until the fifth lunar month of gestation, the fetal body length in centimeters can be obtained by squaring the number of months of pregnancy and after this time by multiplying the months by five.

Fazekas and Kosa, 1978, found that all bones of the fetus could be measured and by the construction of regression curves for each bone, the size of the bone could be related to the size—and hence age—of the corpse as a whole.⁶⁹ This should not be misinterpreted to mean that all bones are of similar value to the forensic investigator. Consider ribs or cranial vault, these are important but are very fragile and destroyed by burial or even drying from water.

WHICH ARE THE BEST BONES TO LOOK FOR?

The requirements are that the bones should be unequivocally identifiable, robust, easily and reproducibly measurable between anatomical landmarks that are easy to find.

Zygomatic Bones

This fulfills all the criteria but are probably not ideal because the relationship between their size and that of the entire fetus is not a simple one.

Basilar Part of the Occipital Bone

An excellent bone for this purpose is the basilar part of the occipital bone. There is only one of these in the body; it looks like nothing else; it is robust and easily measured; moreover, its proportions change with age. If the bone is measured simply in the midline from the front (spheno-occipital synchondrosis) to the notch at the back (foramen magnum) and then at right angles to this between the lateral tubercles to determine its greatest width, then the relationship between these two measurements alone has great significance. At the age of 7 to 7½ lunar months after conception, the width exceeds the sagittal length; prior to this the relationship is the reverse. In many countries, seven lunar months (28 weeks) is considered in law to be the age at which a fetus becomes incipiently (or potentially) viable in its own right.

The Temporal Bone

It is a very useful predictor of age too, even without measurement. It develops from three separate elements; (a) squamous part of vault of skull, (b) petrous part of base of skull; and (c) the tympanic ring (delicate circular bone). At seven lunar months of gestation, all three elements are still separate bones. The fusion of the squamous part with the tympanic ring occurs very soon after this date and may be taken as a morphological sign indicating the viability of the fetus. The fusion of all three elements is complete by 10 lunar months and may be taken as a sign of a full-term fetus.

Mandible

This is perhaps the easiest bone for dentists to identify. This is represented by a separate bone on each side of the face until well into the first year of postnatal life. In fetal period each half of the mandible is always a separate bone. In the early stages of its formation, the mandible is a remarkably straight bone. It is easy to measure from the articular head of the condyle to the symphyseal face at the anterior extremity of the bone. This length in millimeters is always equal to the total crown-heel body length in centimeters: for example, when the mandible is 50 mm in length the fetus is 50 cm long and that occurs at full term. The length of the mandible is one-tenth of the body length during the whole period of intrauterine life. The same relationship holds for radius. Another useful bone with direct relationship is the maxilla, which is one-twentieth the length of the body.

One avenue of research is to examine bone microstructure and chemistry in addition to overall bone and organ morphology. Preliminary work in these areas has already shown age-related differences.

CHRONOLOGY OF DENTAL DEVELOPMENT AND AGE ASSESSMENT

In forensic dentistry, age estimation is not only one of the standard requests upon the discovery of a dead body, but is also critical if identity is in question in living individuals.

Age calculation by means of tooth development and particularly the root formation of third molars has already often proved to be effective in determining an individual's chronologic age. Other methods for age calculation using skeletal radiology (hand-wrist, sternoclavicular joints, long bones and vertebrae) or secondary sex characteristics have at least comparable limitations.⁷⁰

Dental age is estimated by comparing the dental development status of a person of unknown age with published dental development surveys. By doing so, a likely chronologic age for that individual can be deduced. There are also more subtle

ways in which dental development data can be applied. The premineralization and mineralization stages in dental development are well established. The incremental pattern of mineralization is subject to periodic disturbances, which affects the developing teeth in a unique way. Birth, diseases, drug intake, dietary changes and the uptake of certain chemical elements can all cause changes in the incremental pattern. These changes can be detected and, in some instances, be retrospectively linked to a specific time or event during the individual's life.⁷¹

BIOLOGICAL AND CHRONOLOGICAL AGE

Chronologic age: This is the time from birth to the present for a living individual as measured in units of time. However, in the majority of cases in forensic, an individual's biological age is mostly determined.

Biological age: This is an age estimate based on the state of development of the remains quoted in years and months.

Radiographic technique is unable to address the discrepancy between biological and chronological age. As a result radiographs reflect only chronological age. They cannot take into account any acceleration or retardation in the rate of growth or maturation. Histology is the more sensitive technique, early mineralization being detectable up to 12 weeks before it becomes apparent on a radiograph. As such, throughout development, the radiographic appearance of a tooth will be largely behind its anatomical appearance by several months. A radiograph of the first permanent molar will not show significant calcification until approximately six months of age despite beginning of calcification prenatally.

But, studies are conducted with both methods, histologic and radiographic and errorless techniques are being discovered with the help of newer technologies like advanced computer softwares.

Age estimation in forensic dentistry by using important dental developmental milestones

Dentition's maturation is well documented and broadly categorized by three basic processes:

1. Proliferative growth
2. Calcification of crown and root
3. Eruption.

Proliferative Growth

The primary dentition is initiated at approximately 10 weeks *in utero* by a downgrowth of epithelial cells from the oral epithelium in the anterior regions of the jaws to form dental lamina. During the 11th intrauterine week, the differentiation of the tooth bud tissues occurs, i.e. the dental papilla, the outer enamel epithelium, the inner enamel epithelium, the performed

membrane, the stratum intermedium and stellate reticulum. By 12 weeks, the incisors and canines consist of a single conical soft tissue cusp. During the 12th week, the first and second primary maxillary and mandibular molars initiate their soft tissue crown development. Kraus and Jordan summarize the early dental developmental horizons for the primary molars.⁷² At 12½ weeks a distinct bulge occurs on the mesiobuccal portion of the occlusal aspect of the soft tissue crown. This marks the initial appearance of the mesiobuccal cusp. Initial calcification of the first mesiobuccal cusp occurs at 14½ weeks prior to distal cusp development.

The chronologic specificity for the appearance of the successional permanent tooth anlage ranges from about the 20th week *in utero* for permanent incisors to the 10th postnatal month for the second premolars. Proliferative growth by distal extensions from the second primary molar dental laminae begins about the fourth month of fetal life. The permanent molars arise directly from these extensions.

The first permanent molars begin their soft tissue development during the fourth intrauterine month; the first postnatal year for the second permanent molars; and the fourth or fifth year for the third permanent molars.⁷³

Calcification

There is usually an orderly sequence of cusp calcification for primary molars with variations occurring primarily with the distal and distolingual cusps of second primary molars.

The calcification sequences for the primary and permanent cusps, crowns and roots are presented by Schour and Massler. This chart is based on radiographic data. Necessarily, the prenatal timing, in many instances, conflicts with the vital staining data of Kraus and Jordan, which give earlier times for the onset of calcification. (Alizarin red detects initial calcification prior to radiographic observations). Prenatal crown age assessments, based on this chart, must be used with caution.

According to the chart, the primary teeth cusp tips begin to calcify during the 15th week *in utero*. In spite of the early aforementioned problems in initial crown age assessment, the crown completion and root formation data in the Schour and Massler chart are remarkably accurate. Accordingly, coronal calcification is not completed until the end of the first year and root calcification for primary teeth begins about the third to fourth postnatal month and does not end until about the third year.

Permanent tooth crowns (first molars) initiate calcification during the ninth fetal month (Alizarin red). Radiographic evidence shows calcification initiating at birth. Coronal calcification for permanent teeth continues to about 15 to 16 years when third molar crowns complete calcification. Permanent root development begins about the fourth year and continues to about 21 to 23 years.⁷³

Eruption

The third phase of dental development is eruption. Akin to eruption is the shedding of primary teeth during the mixed dentition period. Shortly after the primary roots are completely formed primary root resorption begins. It is important to distinguish between incompletely formed roots and resorbed roots, indeed a difficult task at times.

Primary teeth without successors may or may not show root resorption. If roots are partially resorbed, it is likely that ankylosis will occur. Ankylosed teeth do not maintain capacity for vertical development. Consequently adjacent teeth continue developing vertically leaving the ankylosed teeth in a relatively submerged position.

From the aforementioned discussion, it should be apparent that age can be assessed with a high degree of accuracy up to 20 years of age using events in the developing dentition. Caution must be exercised when using third molar data from the Schour and Massler chart. Little information is provided after 15 years of age.

More importantly, the developmental events may be influenced by racial and/or socioeconomic criteria. Therefore, each forensic dentist should have a reference data base peculiar to the population.⁷³

Age estimation is an important subspecialty of forensic sciences. It also has application in living individuals whose chronologic age is under dispute. Dental age estimation makes use of morphologic, radiographic, histologic and biochemical methods to examine age dependent changes in teeth.

AGE ESTIMATION IN PRENATAL, NEONATAL AND EARLY POSTNATAL CHILD

The primary tooth germ begins to form at seven weeks *in utero* (IU), and the enamel formation of all deciduous teeth is usually complete by the first year. Among the permanent teeth, the first molar shows germ formation first at about 3½ to 4 months IU. The age estimation in this group of individuals can be very accurate. It makes use of histologic techniques, which enable observation of tooth mineralization up to 12 weeks before it is actually apparent on radiographs. The neonatal 'line' is considered as an indicator of birth. Bowers attributes its formation to the slowing down of enamel prism growth rate, thus "creating an apparent line of demarcation". Estimating age in this age group may have legal implications in cases that involve feticide and infanticide.

AGE ESTIMATION IN CHILDREN AND ADOLESCENTS

Nystrom and colleagues consider the estimation of age by study of tooth emergence as a convenient clinical method. It involves

visual assessment of teeth present in the mouth and requires little expertise or equipment. The emergence of deciduous teeth is under genetic control and is relatively regular, commencing approximately at six months and completing by 2½ years. On the other hand, emergence patterns of permanent teeth are under the influence of the intraoral environment, being affected by infection, arch space, and premature tooth loss.⁷⁴

Therefore, evaluation of radiographs to assess tooth calcification is a much better alternative, since:

Calcification of teeth can be observed from the radiographs for a period of several years.

It is not altered by local factors such as lack of space, infection, etc., and the study of tooth calcification also lets us assess age at periods when no emergence takes place (2½–6 years and 12 years).⁷⁴

INCREMENTAL LINES OF CEMENTUM

Evaluation of annual incremental lines of cementum is one of the potentially valuable methods for biological age estimation in forensic anthropology. Biological age was estimated by pooling the number of lines counted and the average age of tooth eruption. It was found that number of lines strongly correlates with chronologic age. Factor of sex has no significant influence on the number of lines. This method is suitable for forensic anthropology and digitalized system enhances the count and provides better result.⁷⁵

There is no known reason for this pattern of incremental lines. There is some speculation regarding changes in quantities of mineral salts laid down and/or differences in growth rates of cemental tissues at different times of the year, resulting in appearance of concentric lines in cementum which can be equated with years.⁷⁵

A reduced rate of cementum apposition was observed in the elderly. Also, maxillary teeth had more cementum on the lingual than on the vestibular surfaces. A tendency was noted for less cementum to occur in women than in men and on teeth removed from deceased persons or extracted for pathologic reasons. The cementum thickness might give a significant contribution to statistical methods of age assessment.⁷⁶

AGE ESTIMATION FROM DENTIN

Bang and Ramm were the first to use dentine translucency alone for estimating age and reported significant increase in root translucency with age. Root dentine starts to become translucent during the third decade of life beginning at the apex and advancing coronally. The alteration is believed to be due to decreased diameter of dentinal tubules caused by increased intratubular calcification. Hence, difference in refractive indices between intratubular organic and extratubular inorganic material is equalized, resulting in increased translucency of the

affected dentine. For example, Solheim suggested translucency, length (mm) or area (mm²) may be measured on intact or sectioned teeth.⁶

The amount of secondary dentin in a tooth has been used as one of several parameters in methods for age estimation.⁷⁷ Dentin deposition has been measured according to various scoring systems and the Pearson correlation coefficient with age has been found to be approximately 0.6. A tendency was also observed towards reduced speed of secondary dentin formation in the elderly and in women.⁷⁸

The amount of sclerotic root dentine increases with age, proceeding from the apex towards the crown. There are obvious optical changes in the tissue, which becomes translucent (dentin is normally opaque). Therefore, sclerosis of root dentin could be a reliable indicator of age in anthropological studies of human remains. Qualitative analysis was performed with polarized light microscopy and measurements were made with a quote 2D, x, y viewer and on digital images.⁷⁹

Age related changes in tooth color have been described previously. Age can be estimated by objective measurement of dental color using spectroradiometry. The determination of dentin color by spectroradiometry is a potentially useful objective method to estimate age in forensic studies in combination with other methods.⁸⁰

REVIEW OF THE VARIOUS DEVELOPMENT SURVEYS

Dental developmental surveys are packaged in different ways; they give us two types of information:

- The sequence of developmental events;
- The timing at which these events are said to occur.

Dental age assessment may be described as an '*educated approximation*' based on developmental surveys that are designed to solve clinical rather than forensic problems. Some of these surveys, which can be used for forensic purposes, are reviewed below.

COMMONLY USED SURVEYS

Schour and Massler

The surveys of **Schour and Massler, 1941**, have their origin in the work of **Logan and Kronfield, 1933**. In **1935**, **Schour and Massler** published a numerical development chart for the deciduous and permanent teeth. The Schour and Massler surveys appeal is obvious; both developing dentitions are displayed *in situ*, and it includes root resorption sequences for the deciduous teeth. As the drawings are life-size, it is easy to make direct comparisons with either radiographs or individually removed developing teeth. This has been discussed earlier.

Moorees, Fanning and Hunt⁸¹

This method used and tabulated data thus making the survey of **Moorees et al 1963**, a useful development standard for the forensic dentist. Another study by Anderson et al. 1976, using a different sample and radiographic view but the same mineralization criteria, allows a useful comparison between two geographically close but different population groups.

Advantage: Between these two studies, development data are available for each individual developing permanent tooth.

Moorees et al defined 14 stages of mineralization for developing single and multirrooted permanent teeth. The results are expressed as the mean age of attainment for each of the 14 stages for developing teeth studied, ± 2 standard deviations. The crown formation stages show less variation when compared with root formation stages; this should be kept in mind when accuracy is of prime importance. The earliest age in surveys is 6 months, and the data include development of the third mandibular molar.⁸¹

Points of forensic interest from this study are:

- Sex difference in crown formation stages is minimal. Differences of development in sexes are apparent in root formation, where females developed ahead of males.
- The teeth emerge clinically at R $\frac{3}{4}$ stage.
- Greatest sexual dimorphism is expressed in the mandibular canine, females being up to 11 months in advance of males with this particular tooth.⁷¹

Anderson, Thompson and Popovich⁸²

Anderson et al 1976, applied the criteria of Moorees et al in a longitudinal study using cephalometric radiographs. All developing teeth were rated including third molars.

According to **Fanning, 1961**, interobserver variation is found in as many as 27 percent of sample ratings, but is usually confined to plus or minus one stage. This fact highlights one of the difficulties in using a rating system with so many stages, which might lead to a debate in court as to where one stage begins and another ends. A modified presentation package using the 14 stage mineralization criteria is given.⁷¹

Demirjian, Goldstein and Tanner⁸³

In this method of **Demirjian et al (1973)**, each stage of mineralization is given a score, which provides an estimate of dental maturity on a scale 0 to 100. The mathematics and rationale used to calculate the scores are those of **Tanner et al 1983**.⁸⁴ Eight stages of dental development are depicted by published radiographic surveys, supplemented with a written description of the limits of each stage of mineralization which are clearly defined and do not require

absolute measurements. This system is most highly developed of all dental age surveys.

There are two options when using this method, one involving the rating of seven mandibular teeth (Demirjian, 1978) and the second using four mandibular teeth (Demirjian and Goldstein, 1976). Missing teeth from one side can be substituted by those from the other side. If first molar is absent, the central incisor can be substituted (Demirjian, 1978). Griffin and Malan (1987) reviewed this system and produced a pocket version of the system, which can be used in field.

Data obtained using Demirjian system indicates that dental developmental differences between males and females are not usually apparent until age of 5 years. Inter-observer variation with this system is as high as 20 to 25 percent.⁷¹

Disadvantages: It does not include the developing third molars. The reliance on mandibular tooth rating can be a problem in skeletonized remains where often the mandible disarticulates and is lost. **Griffin and Malan, 1987**, concluded that eight-stage system was less prone to examiner error.⁷¹

This method is also applicable for Indian Population as in agreement with Nanda and Chawla, 1966 and Demirjian, 1971, who reported that dental formation of French-Canadian children closely correlated with Lucknow (India) children.⁸⁵

Demirjian and coworkers developed an age estimation method that made use of a scoring system.⁸⁶ The development of seven mandibular teeth on the left side was divided into eight stages each. These stages were named 'A' to 'H'. While the third molars were not used in the original method, a recent study by Chaillet and Demirjian accommodates them. Each tooth is assigned a 'maturity score' that corresponds to its developmental stage. The maturity score assigned for each tooth is added and a total maturity score obtained. This total maturity score is then plotted on a chronological 'age conversion table'. Bearing in mind the differences in dental development between boys and girls, the authors provided separate maturity scores and age conversion tables for both sexes.

Gustafson

Gustafson, 1966, developed a comprehensive compact chart of dental development for forensic use, using four stages of development, the data being derived from a comprehensive review of the literature. The chart does not differentiate between males and females.⁷¹

In 1950, **Gosta Gustafson** developed a method for age estimation based on morphological and histological changes of the teeth.⁸⁷ This assessed regressive changes such as:

- Amount of occlusal attrition (A).
- Coronal secondary dentine deposition (S).
- Loss of periodontal attachment (P).
- Cementum apposition at the root apex (C).

- Root resorption at the apex (R).
- Dentine translucency (T).

For each of these regressive changes or variables, different scores ranging from 0 to 3 were assigned. This meant attrition could have any one of four scores (A0, A1, A2, or A3) and similar one of the four scores for other variables. Adding the allotted score for each variable (e.g. A3 + S2 + P2 + C1 + R2 + T1 = X), a total score was obtained. It was found that an increase in the total score (X) corresponds to an increase in age. Age was estimated using the formula

$$\text{Age} = 11.43 + 4.56X.$$

Maples and Rice found that there was a miscalculation in the above formula, and proposed a correction:

$$\text{Age} = 13.45 + 4.26X.$$

However, the improvements made by Johanson are widely accepted. Instead of the original four grades (0–3), he proposed seven grades (0, 0.5, 1, 1.5, 2, 2.5, and 3). Using these seven grades, the formula:

$$\text{Age} = 11.02 + (5.14A) + (2.3S) + (4.14P) + (3.71C) + (5.57R) + (8.98T) \text{ was suggested.}$$

Van der Linden and Duterloo

Moving away from radiographic surveys, van der Linden and Duterloo, 1976, produced an atlas of development of human dentition spanning the period from birth to completion, at yearly intervals. The atlas is a photographic presentation supplemented with diagrams.⁷¹

Third Molar Development

The tooth most commonly missing in man is the third permanent molar.⁴⁰

After the age of approximately 14 years, the third molar is the only developing tooth and assumes great forensic significance. At or after this age, whether clinically visible or not, its status should always be investigated. Its morphology and clinical presentation make it the most variable of the permanent teeth. Its development is prone to wide temporal fluctuations. The data of **Moorees et al 1963**, indicate that the crown formation stages of this tooth display less variation than the root formation stages.⁸¹ **Anderson et al 1976**, held an opposite view.⁸² **Ciapparelli, 1985**, found an almost constant variation of about ± 1 year for both root development and crown formation stages.⁶¹ Therefore, it cannot be assumed that variation during development of this tooth is greater than that of other developing teeth. **Johanson, 1971, Harris and Nortje, 1984, and van Heerden, 1985**, all used a similar five-stage system of root development in their studies of root formation for the third molar. Their findings indicated insignificant

differences in third molar development between the four quadrants and no sexual difference.⁷¹

Gleiser and Hunt method consists of a 10-stage development scale, with three stages for crown formation and seven for root development. When **Mesotten et al** used Gleiser and Hunt method, the results revealed standard deviations similar to those reported in comparable publications and even to those calculated with other skeletal age calculation techniques.⁸⁸

FORENSIC PHOTOGRAPHY

Accurate photography is crucial to forensic investigation as a means of documenting evidence. The need to photographically record injury patterns on skin is paramount to the odontologists and pathologists.

The process of photographically recording images on film, videotape or other media occurs through the capture of electromagnetic radiation (light) of specific wavelengths.

Photographic films are sensitive to light wavelengths in the range of 250 to 900 nm. Visible light comprises the range of electromagnetic radiation from 400 to 760 nm. Most modern camera equipment and film is specifically designed to record images seen in the visible range of light.

It is also possible to record images specifically illuminated in the shorter ultraviolet range (210 to 400 nm), and longer infrared range (750 to 900 nm). Wavelengths of lights that are outside visible range of electromagnetic radiation are commonly referred to as 'nonvisible light'. Photography using nonvisible light requires special techniques to record the injury. It also requires minor focusing adjustments called as 'focus shifts'.

When light strikes skin, four basic events occur (1) reflection (2) absorption (3) transmission and (4) fluorescence. These events occur simultaneously when light strikes human skin. Depending on the wavelength of the source of the incident light and the configuration of the camera, it is possible to record, individually, any of the four reactions of skin to light energy.⁴⁵

GENERAL CONSIDERATIONS

In almost all photographic work intended for legal purposes, the following considerations apply:

- Photographs should be made in duplicate, anticipating that one set may have to be surrendered as permanent courtroom evidence.
- Bracketing the exposures is prudent and will buffer slight exposure errors due to mechanical failure or human miscalculation.
- Using varied perspectives to make photographs is advisable, particularly because the electronic flash may produce unpredictable and often unpleasant reflections.
- The recording of data (date, time, location, case number, camera, lens, aperture, film, light source, subject distance) helps reconstruct cases.

- Consistency and reproducibility of techniques and results are more important than artistic composition.
- The use of Kodak processing laboratories for color film is an assurance of quality control, standardization and legal acceptability.

PHOTOGRAPHY IN DENTAL IDENTIFICATION⁴⁵

Types of Photography

- *Visible light photography:*
 - Visible light color photography
 - Visible light black and white photography.
- *Alternate light imaging and fluorescent techniques:*
- *Nonvisible light photography:*
 - Reflective long-wavelength ultraviolet (UV) photography
 - Infrared photography.

Suggested Photographs to be Taken⁸⁹

In situ full body photographs: These views could be important since they provide a version of the untampered evidence and ensure that any subsequent manipulation has not concealed or destroyed information. These photographs are of greatest concern when one attempts to reconstruct mass disasters and bite mark cases.

Full face and profile photographs: These photographs would be useful in instances in which body is well preserved and is identifiable visually.

Photographs of anterior teeth: Close-up photographs of the exposed anterior teeth are important in case the only antemortem record that materializes is a photograph of the victim smiling. Also, postmortem photographs are useful when carbonization of anterior teeth threatens their preservation.

Photographs of resected jaw specimens or skeletonized jaws: If jaws are removed, following series should be made:

- View of all recovered portions of maxilla and mandible;
- Close-up occlusal view of mandible;
- Close-up palatal view of maxilla;
- Anterior view of articulated jaws (if possible);
- Left and right lateral views of articulated jaws (if possible);
- Any additional photographs necessary to demonstrate a peculiarity not seen to advantage in other views.

Photographs of antemortem radiographs: These photographs are helpful when radiographic duplicates are unavailable or when originals cannot be retained by the forensic dentist. Photographs of antemortem and postmortem radiographs mounted in tandem on same exposure provide an effective tool to demonstrate concordance in court.



FIGURE 15.15: A single lens reflex 35 mm camera with 100 mm focal length lens, exchangeable extension rings and ring-flash is usually adequate

Photographic Equipment:⁹⁰

1. 35 mm SLR cameras (Nikon 35 mm or digital cameras) (Fig. 15.15)
2. Electronic flash gun
3. Cable release
4. Metal measuring tape
5. Angle setter
6. Beanbags
7. Grey scale card/color/monochrome patches
8. Framing attachment/lens
9. Tripod
10. Film (color and monochrome)
11. Lens hood
12. Rigid scales (photographic)/ABFO #2
13. Disc (photographic)
14. Writing materials.

Procedure

Consent: It is of vital importance that consent, in writing, is obtained from the subject prior to the commencement of any photography.

Method

A comfortable working position for both victim and photographer is achieved by supporting the part being photographed on strategically placed beanbags. The camera must be mounted on a sturdy tripod with pan and tilt facility and lateral arm. The flashgun is connected to the camera such that the shutter speed is set at appropriate synchronization.

For identification purposes a general photograph is taken of the entire subject, this includes facial features and gray scale card with color or monochrome patches attached.

Bite mark photographs without any scale present to prove that nothing of evidential value will be obscured when scales are applied. Rigid self-adhesive scales are introduced for remaining photographs. These are assembled at right angles

to each other and placed close to and in plane of the bite mark ensuring that they are not obscuring any part of mark.⁹⁰

Camera Positioning

Flat surface photography: The film plane is made parallel to the scale by placing the angle setter on the scale and rotating the adjustable vial until the bubble is centered. The angle setter is then moved back to the camera and the camera adjusted laterally until the bubble is centered—the film plane is now parallel to the scale. To position the lens perpendicular to the scale, the angle setter is turned through 90 degrees and replaced on the scale.

Curved surface photography: Each dental arch is photographed individually. When photographing curved surfaces, the above procedures are followed, in addition to which a 5-degree adjustment is made, using the angle setter graduations, so that the lens is aimed from outside of the arch at a point in the central part of the curve. It is important to note that the overlays are life-size and distortion-free and that mismatches with photographs are due to photographically induced errors where they are not due to tissue behavior.

Recording the Images

Films: The light sensitive materials used in forensic dental photography are a matter of personal preference.⁹⁰

Film manufacturers have designed photographic films that record light wavelengths from 250 to 700 nm. Special infrared films are available that can record photographs taken in light from 250 to 900 nm. Correct film speed must be determined. Films come with a rating, referred to as the ASA/ISO number, which serves as an indicator of the amount of light energy necessary to properly expose the film. The higher the ASA/ISO number, faster the film, in other words less light is needed to expose an image.

Digital photography utilizes a special computer hard disk in the camera that stores the images as digital information. These images can be later written to a CD-ROM for storage. Advantage is that the image can then be immediately viewed on a computer monitor or printed on a color printer.⁴⁵

Light Source Placing

To achieve optimum reproduction of bite marks, which leave very slight impressions, the light source must be positioned at 45-degree angle to the mark. The aim is to achieve oblique illumination of the irregularities in the tissue surface.

Bite Marks in Food and Other Material

Photography of bite marks on inanimate objects is taken with a rigid scale. It is important to obtain a control sample of food and to swab the bitten food for saliva traces. It is also important

that food be removed from the refrigerator early enough, prior to photography, to prevent condensation of water vapor spoiling the detail in the picture.

Photographic Reproduction of Overlays

The photographic transparency technique is the most accurate method of producing overlays for comparison purposes. The production of the transparency involves emphasizing the incisal and cuspal edges of the teeth of a duplicate set of dental models with a fine, indelible black marker pen. In order to produce high-contrast line transparency, the models are placed on an illuminated light box and a photograph taken using a lithographic emulsion. A rigid scale must be placed in the plane of the teeth to ensure accurate 1:1 reproduction.⁹⁰

Photography of Faces, Dental Models, Dentures and Dissected Jaws

Photographs of faces for record purposes should be taken prior to the commencement of any postmortem dissections. It may be necessary to photograph faces, dental models, dentures or dissected jaws as part of the evidential photography to be produced in court. A rigid scale is fixed in plane of the teeth when taking photographs. Color photographs show the colors of the teeth, gums and restorations, often assisting with identification of the victim. Photographs of dentures, especially those that show laboratory or identification marks are most useful and can be included in the professional publications when requesting information as to the identity of the owner.

Photographs of Teeth

For record purposes it may be necessary to photograph anterior teeth or intraoral pictures. Use of ring flash is more convenient in these cases and for intraoral photography a set of front reflecting mouth mirrors is necessary. A conventional 35 mm camera may be used for this purpose.⁹⁰

Handling of Photographic Evidence

The photographs documenting a victim's injuries may become part of the legal system and, as such, are subject to 'chain of evidence' rules. This requires accountability as to what individuals had possession of the evidence from the time it was collected until it is marked and introduced into the legal system. Categorizing system usually consists of numbers or letters which include the case number, as well as an identifying mark of the forensic photographer. This can be his or her initials or signature, so that photographs can be identified as originals and the chain of evidence maintained. Photography is one of the important protocols of forensic dentistry. Developing skills

necessary to competently document these injuries with visible and nonvisible light is one of the great challenges in forensic dentistry.

ROLE OF FORENSIC DENTISTRY IN MASS DISASTERS

The world has experienced a plethora of mass disasters in recent years—hurricanes, earthquakes, floods, typhoons, mud slides, transportation mishaps, aircraft mishaps, fires, volcanic eruptions, industrial accidents, terrorist acts and armed conflicts. In addition to naturally occurring disasters, as the world population increases, technology expands and life becomes more complicated. As a result, we may anticipate more untoward events generated by people. The role that forensic dentistry and the forensic science community play in such disasters varies with jurisdiction throughout the world.⁹¹

In five mass disasters handled by the British team between 1985 and 1989, involving over 1000 victims, dentistry contributed to identification in just over 80 percent.⁴²

Recently, 26 December 2004 saw devastation and loss of life around the Indian ocean. Till date 1,474 deceased have been identified. Dental comparison has been the primary identifier in 79 percent of cases and a contributor in another 8 percent, a total of 87 percent.⁹²

The identification of human remains in mass disasters allows surviving family members to go through the grieving process; place legal, business and personal affairs in order, and continue with the processes of life.

DISASTER SITE MANAGEMENT⁹¹

In the recovery phase of the disaster, a 500 to 2000-ft security cordon should be established outward from the disaster site. An entry control point for the cordon is placed. An access list is developed and all personnel within the cordon must wear identification badges. These actions are necessary to protect disaster evidence, staff, and bystanders. The team should carefully search the site for human remains or fragments (Fig. 15.16). Fragmentation and commingling of remains will be a major problem with high impact force mishaps. A body recovery tag should be placed on each specimen. The numbering system should be as simple as possible. The use of computers and bar code readers can be most helpful from the beginning in remains/fragments tracking, documentation and management.

Once the body has been prepared, it is placed in a recovery bag for transport to the identification center. The remains should be removed to the Identification Center and refrigerated to approximately 37° F as soon as possible. Once all the remains have been removed from the site, it is wise to repeat the overlapping ground search. Surprisingly, large volume of body



FIGURE 15.16: Collection of evidence at the site of mass disaster

fragments and personal effects will be located with the second effort.

DISASTER MANAGEMENT

In most jurisdictions, there are three or four legally admissible methodologies used to identify human remains:

1. Visual identification.
2. Fingerprints or footprint identification.
3. Dental identification.
4. DNA evidence.

Among these methods visual identification is least reliable due to subjective factors and stressful situation in which a relative or friend is placed. Fingerprint mode is long respected, but is subject to availability of antemortem prints on file. Dental identification is also subject to available antemortem dental records and radiographs. DNA comparison is legally admissible in a growing number of jurisdictions. If immediate relatives of the victim are available, the genetic makeup may be established without an antemortem DNA record of the victim being on file.

FORENSIC IDENTIFICATION CENTER ORGANIZATION⁹³

Past disaster experiences have shown that a multidisciplinary disaster Identification Center with a forensic sciences processing line is highly effective in the identification of large numbers of human remains. The success of this organization is keyed to preplanning, cooperation and smooth communications between all sections. Data flow between all sections must be orderly to enable each section to capitalize on what other sections have learned. For example, time can be saved if the Forensic Dentistry Section knows that the 'Personal Effects

Section' has found a name in an article of clothing or a military identification tag on a particular body. The status of human remains may be thought to be in three categories: (1) positive identification; (2) findings consistent between antemortem and postmortem records; and (3) unidentified. Registrar, computer services, communication services, public affairs, mortuary service, security and support services are critical sections supporting the Identification Center chief and the various forensic science sections. The source of information emanating from the Identification Center must be either the Identification Center chief or the Public Affairs officer.

Forensic Dentistry Section

A Forensic Dentistry Section should be an integral part of the organization of the disaster Identification Center. The Forensic Dentistry Section should be divided into three subsections and should be headed by a team chief responsible to the Identification Center chief. The role of Forensic Dentistry Section chief is that of manager, facilitator, coordinator and spokesperson for the section.

*Postmortem dental examination and dental radiology subsection:*⁹¹ The role of this section is straightforward and uncomplicated of the three subsections. A forensic photographer should be available to provide photographic support during postmortem examinations. The first part of dental team, made up of oral surgeons, accomplishes the necessary facial dissection to allow the oral cavity to be visualized and radiographed. After facial dissection has been accomplished, the remains are moved to the next area within the postmortem dental examination subsection for dental radiographs.

A full-mouth postmortem dental radiographic series is accomplished utilizing a portable dental X-ray unit. A 50-kVP dental radiographic instrument is quite adequate since normal exposure factors can generally be reduced by one quarter to one half when working with severely burned victims because of water loss from the body.

The use of automatic dental X-ray film processors with daylight loading hoods is recommended. Dental radiographs provide objective evidence that is essential within the scientific community and in court. Flat plate radiographs of the entire body, although expensive, provide significant medical and anthropological evidence and are an excellent tool for locating personal effects and dental fragments in commingled, charred remains.

After a thorough cleaning of dental structures with a dilute bleach solution, a team of three dentists, or two dentists and a dental hygienist or assistant, charts all dental evidence on a postmortem dental record form. The universal numbering system is preferred because it is simple in nature and is easily

computerized. The use of a fiber-optic light is invaluable in the examination process.

The examiner begins by evaluating both tooth #1 and associated radiographs. The second dentist on the examination team evaluates tooth #1 and confirms the findings of the tooth #1 and all three team members confirm the charting. Errors are corrected in a legally acceptable fashion.

Confusion should be avoided on extracted or congenitally missing teeth. In some cases, prosthetic appliances may have been specifically marked for identification. It is wise to solicit, from the victim's dentist or family, study models or extra prosthetic appliances, which may be available. Such evidence is important in providing antemortem data regarding ridge shape/size, rugae patterns and general oral anatomy.

*Antemortem record subsection:*⁹¹ Dentists, hygienists, skilled dental assistants and dental investigators can effectively operate this subsection. The task of this section will always be most difficult in the entire forensic dentistry arena.

It is clearly necessary to reduce all antemortem dental evidence to a single antemortem dental record form in order to provide a composite antemortem picture. Photographs of possible fatalities are often received by this subsection. They may be of value in demonstrating malocclusions and other facial and dental anatomy. The anthropologist and forensic artist will also find these photographs of value. Carefully mark the reverse of these photographs with the name and address of the provider.

*Postmortem dental records/computers and comparison subsection:*⁹¹ This is the third part of the Forensic Dentistry Section. Postmortem dental records and completed antemortem composite dental records are forwarded to this section. The task of this section is comparison of antemortem and postmortem examination and radiographic findings. This section must also keep abreast of the findings of all forensic sections within the Identification Center and apply their findings in dental comparison process.

If the subsection operates without a computer, the size of the section is dependent on the number of fatalities, since there is a requirement to place all postmortem dental records face-up on tables in numerical order for a comparison with the antemortem composite dental records as they are received with the postmortem dental records placed on the table. Once significant points of comparison are noted, radiographs of the respective records can be reviewed and a possible identification established. Time is a major consideration. A dental identification form which summarizes the identification data can be completed at this time. Only after all sections have presented their evidence and all inconsistencies have been explained should the Identification Center chief sign the case

out as positive identification. After the case has been signed out as positive identification, the antemortem and postmortem dental records and associated evidence should be combined with the summary sheet into a single completed file.

A Computer-Assisted Postmortem Identification System (CAPMI) designed by Colonel Lewis Lorton and Mr. William H Langley, represents latest development of an identification system utilizing today's technology.⁹⁴ The system provides efficient management of data. It permits comparing statistically significant and related antemortem and postmortem records. Due to its inherent high selectivity, it can also overcome many human errors in the database.

The CAPMI System, Northwestern University system and the Mertz and Purtilo system are examples of available computer programs in forensic dentistry.

CONCLUSION

Each practitioner has a responsibility to understand the forensic implications associated with the practice of his or her profession. This understanding should include more than ethics and jurisprudence, which were traditionally the only aspects of a dentist's knowledge of the law. Appreciation of forensic dental problems permits clinicians to maintain legally acceptable records and assist legal authorities in the identification of victims of disasters and crimes.

Dental surgeons around the world can contribute significantly in solving crime, identifying victims of mass disaster and understanding of prehistoric man by giving due importance to the subject of Forensic Odontology. The science needs necessary inputs in the form of formal training, job allocation and research by the profession if it is to play an active role in criminology and allied fields. Utilization of computers and newer technology hold promise for the advancement of Forensic Odontology as an area of specialization that needs to be taken up on a priority basis.

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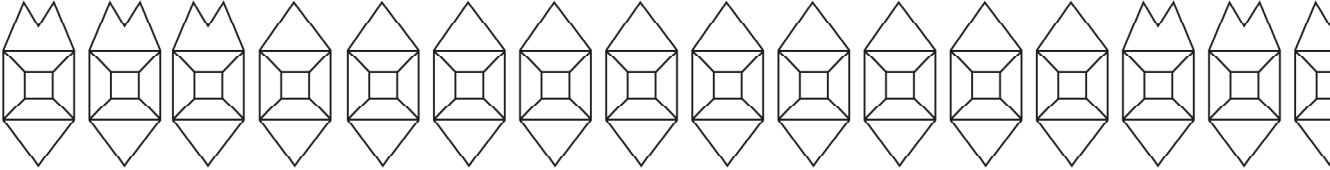
Annexure 1: Postmortem dental examination

DENTAL EXAMINATION OF DECEASED

To be completed for each deceased aircrew member and where indicated for deceased passengers:

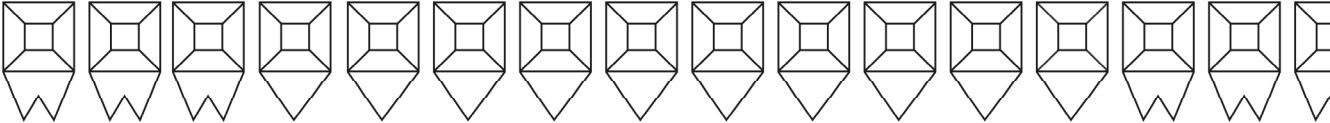
Rank				Name				Number			
Crew Duty (or passenger seating)								Date			
Body number				Location after crash							
Time		(a) of crash		(b) death			(c) autopsy				

1



R 8 7 6 5 4 3 2 1 1 2 3 4 5 6 7 8

4



Dentures															
Soft tissue examination															
Remarks and identification criteria															

Australian armed forces form for
the dental examination
of deceased aircrew and passengers

Annexure 2: Antemortem and Postmortem Dental Records

Health commission of New South Wales Dental Identification Record

A. Case History:

B. Examination Date: ____/____/____

Site of Examination:.....

Requested by:.....

Examiner's Name and Position:

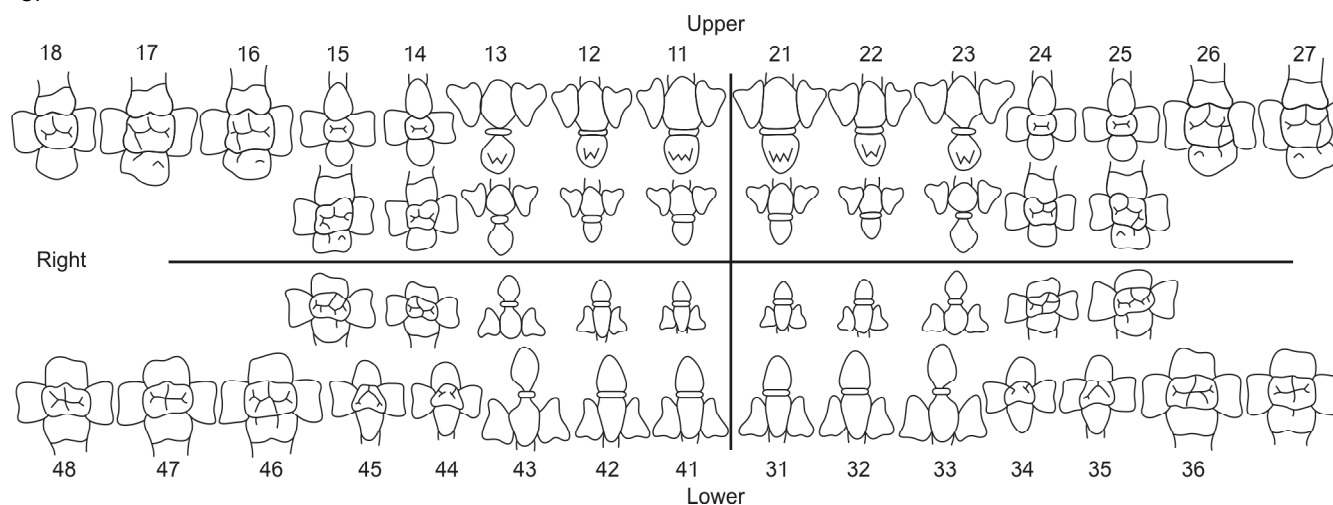
Post-mortem dental
photographs:

Yes	No
-----	----

Post-mortem dental
X-rays

Yes	No
-----	----

C.

Part 1 of the Health commission of NSW
dental identification record

D.

Upper right	Upper left	Lower left	Lower right
1.8	2.8	3.8	4.8
1.7	2.7	3.7	4.7
1.6	2.6	3.6	4.6
1.5	2.5	3.5	4.5
1.4	2.4	3.4	4.4
1.3	2.3	3.3	4.3
1.2	2.2	3.2	4.2
1.1	2.1	3.1	4.1

SUBSTITUTE QUADRANT NUMBER FOR DECIDUOUS TEETH

E. Appliances (prosthetic including bridgework, orthodontic, surgical)

Maxilla—

Mandible—

F. Ante-mortem records obtained from:

Name:..... Address:.....

Describe ante-mortem records:.....

Additional Notes on Back:

Yes	No
-----	----

Signature of Examiner

Part 2 of the Health Commission of
NSW Dental Identification Record



Appendices

NORMAL LABORATORY VALUES FOR CHILDREN

Sr. No.	Age range	Normal values
BLOOD CHEMISTRY		
1. Albumin	0-1 year 1 year to adult	2.0-4.0 g/dL 3.5-5.5 g/dL
2. Ammonia	Newborns Children Adults	90-150 mcg/dL 40-120 mcg/dL 18-54 mcg/dL
3. Amylase	Newborns Adults	0-60 units/L 30-110 units/L
4. Bilirubin, conjugated, direct	Newborns 1 month to adult	<1.5 mg/dL 0-0.5 mg/dL
5. Bilirubin, total	0-3 d 1 month to adult	2.0-10.0 mg/dL 0-1.5 mg/dL
6. Bilirubin, unconjugated indirect		0.6-10.5 mg/dL
7. Calcium	Newborns 0-2 years 2 years to adult	7.0-12.0 mg/dL 8.8-11.2 mg/dL 9.0-11.0 mg/dL
8. Calcium, ionized, whole blood		4.4-5.4 mg/dL
9. Carbon dioxide, total		23-33 mEq/L
10. Chloride		95-105 mEq/L
11. Cholesterol	Newborns 0-1 year 1-20 years	45-170 mg/dL 65-175 mg/dL 120-230 mg/dL
12. Creatinine	0-1 year 1 year to adult	0.6 mg/dL 0.5-1.5 mg/dL
13. Glucose	Newborns 0-2 years Children to adults	30-90 mg/dL 60-105 mg/dL 70-110 mg/dL

Sr. No.	Age range	Normal values
14. Iron	Newborns Infants Children Adults	110-270 mcg/dL 30-70 mcg/dL 55-120 mcg/dL 70-180 mcg/dL
15. Iron binding	Newborns Infants Adults	59-175 mcg/dL 100-400 mcg/dL 250-400 mcg/dL
16. Lactic acid, lactate		2-20 mg/dL
17. Lead, whole blood		<10 mcg/dL
18. Lipase	Children Adults	20-140 units/L 0-190 units/L
19. Magnesium		1.5-2.5 mEq/L
20. Osmolality, serum		275-296 mOsm/kg
21. Osmolality, urine		50-1400 mOsm/kg
22. Phosphorus	Newborns 6 weeks to 19 months 19 months to 3 years 3-15 years > 15 years	4.2-9.0 mg/dL 3.8-6.7 mg/dL 2.9-5.9 mg/dL 3.6-5.6 mg/dL 2.5-5.0 mg/dL
23. Potassium, plasma	Newborns 2 days to 3 months 3 months to 1 year 1-16 years	4.5-7.2 mEq/L 4.0-6.2 mEq/L 3.7-5.6 mEq/L 3.5-5.0 mEq/L
24. Protein, total	0-2 years > 2 years	4.2-7.4 g/dL 6.0-8.0 g/dL
25. Sodium		136-145 mEq/L

Sr. No.	Age range	Normal values
26. Triglycerides	Infants Children Adults	0-171 mg/dL 20-130 mg/dL 30-200 mg/dL
27. Urea nitrogen, blood	0-2 years 2 years to Adult	4-15 mg/dL 5-20 mg/dL
28. Uric acid	Male Female	3.0-7.0 mg/dL 2.0-6.0 mg/dL
ENZYMES		
1. Alanine aminotransferase (ALT) (SGPT)	0-2 months > 2 months	8-78 units/L 8-36 units/L
2. Alkaline phosphatase (ALKP)	Newborns 0-16 years >16 years	60-130 units/L 85-400 units/L 30-115 units/L
3. Aspartate aminotransferase (AST)	Infants	18-74 units/L
4. Serum glutamic oxaloacetic transaminase (SGOT)	Children Adults	15-46 units/L 5-35 units/L
5. Creatine kinase (CK)	Infants Children Adult male Adult female	20-200 units/L 10-90 units/L 0-206 units/L 0-175 units/L
6. Lactate dehydrogenase (LDH)	Newborns 1 month to 2 years >16 years	290-501 units/L 110-144 units/L 60-170 units/L

SERUM LIPID CONCENTRATIONS BY AGE AND GENDER

	Males (mg/dL)			Females (mg/dL)		
	5-9 years	10-14 years	15-19 years	5-9 years	10-14 years	15-19 years
TOTAL CHOLESTEROL						
50th percentile	153	161	152	164	159	157
75th percentile	168	173	168	177	171	176

	Males (mg/dL)			Females (mg/dL)		
	5-9 years	10-14 years	15-19 years	5-9 years	10-14 years	15-19 years
90th percentile	183	191	183	189	191	198
95th percentile	186	201	191	197	205	208

TRIGLYCERIDES

50th percentile	48	58	68	57	68	64
75th percentile	58	74	88	74	85	85
90th percentile	70	94	125	103	104	112
95th percentile	85	111	143	120	120	126

LDL-C

50th percentile	90	94	93	98	94	93
75th percentile	103	109	109	115	110	110
90th percentile	117	123	123	125	126	129
95th percentile	129	133	130	140	136	137

HDL

5th percentile	38	37	30	36	37	35
10th percentile	43	40	34	38	40	38
25th percentile	49	46	39	48	45	43
50th percentile	55	55	46	52	52	51

Adapted from American Academy of Pediatrics Committee on Nutrition, "Lipid Screening and Cardiovascular Health in Childhood". Pediatrics, 2008;122:(1)198-208.

THYROID FUNCTION TESTS

Sr. Hormone No.	Age	Concentration
1. T4 (thyroxine)	1-7 day 8-14 day 1 month to 1 year > 1 year	10.1-20.9 mcg/dL 9.8-16.6 mcg/dL 5.5-16.0 mcg/dL 4.0-12.0 mcg/dL
2. FTI	1-3 day 1-4 week 1-4 month 4-12 month 1-6 year > 6 year	9.3-26.6 7.6-20.8 7.4-17.9 5.1-14.5 5.7-13.3 4.8-14.0
3. T3	Newborns 1-5 year 5-10 year 10 years to Adult	100-470 ng/dL 100-260 ng/dL 90-240 ng/dL 70-210 ng/dL
4. T3 uptake		35-45%

contd...

contd...

Sr. Hormone No.	Age	Concentration
5. TSH	Cord 1-3 day 3-7 day > 7 day	3-22 micro international units/mL < 40 micro international units/mL < 25 micro international units/mL 0-10 micro international units/mL

BLOOD GASES

Sr. No.	Arterial	Capillary	Venous
1. pH	7.35-7.45	7.35-7.45	7.32-7.42
2. pCO ₂ (mm Hg)	35-45	35-45	38-52
3. pO ₂ (mm Hg)	70-100	60-80	24-48
4. HCO ₃ (mEq/L)	19-25	19-25	19-25
5. TCO ₂ (mEq/L)	19-29	19-29	23-33
6. O ₂ saturation (%)	90-95	90-95	40-70
7. Base excess (mEq/L)	5 to +5	5 to +5	5 to +5

HEMATOLOGIC VALUES

Sr. No.	Age	Hgb (g/dL)	Hct (%)	RBC (mill/mm ³)	RDW	MCV (fL)	MCH (pg)	MCHC (%)	PLTS (x10 ³ /mm ³)
1.	0-3 days	15.0-20.0	45-61	4.0-5.9	<18	95-115	31-37	29-37	250-450
2.	1-2 weeks	12.5-18.5	39-57	3.6-5.5	<17	86-110	28-36	28-38	250-450
3.	1-6 months	10.0-13.0	29-42	3.1-4.3	<16.5	74-96	25-35	30-36	300-700
4.	7 months to 2 years	10.5-13.0	33-38	3.7-4.9	<16	70-84	23-30	31-37	250-600
5.	2-5 years	11.5-13.0	34-39	3.9-5.0	<15	75-87	24-30	31-37	250-550
6.	5-8 years	11.5-14.5	35-42	4.0-4.9	<15	77-95	25-33	31-37	250-550
7.	13-18 years	12.0-15.2	36-47	4.5-5.1	<14.5	78-96	25-35	31-37	150-450
8.	Adult male	13.5-16.5	41-50	4.5-5.5	<14.5	80-100	26-34	31-37	150-450
9.	Adult female	12.0-15.0	36-44	4.0-4.9	<14.5	80-100	26-34	31-37	150-450

WBC AND DIFFERENTIAL LEUKOCYTE COUNTS

Age	WBC (x10 ³ mm ³)	Segs	Bands	Lymphs	Monos	Eosinophils	Basophils	Atypical Lymphs	No. of NRBCs
0-3 days	9.0-35.0	32-62	10-18	19-29	5-7	0-2	0-1	0-8	0-2
1-2 weeks	5.0-20.0	14-34	6-14	36-45	6-10	0-2	0-1	0-8	0
1-6 months	6.0-17.5	13-33	4-12	41-71	4-7	0-3	0-1	0-8	0
7 months to 2 years	6.0-17.0	15-35	5-11	45-76	3-6	0-3	0-1	0-8	0
2-5 years	5.5-15.5	23-45	5-11	35-65	3-6	0-3	0-1	0-8	0
5-8 years	5.0-14.5	32-54	5-11	28-48	3-6	0-3	0-1	0-8	0
13-18 years	4.5-13.0	34-64	5-11	25-45	3-6	0-3	0-1	0-8	0
Adults	4.5-11.0	35-66	5-11	24-44	3-6	0-3	0-1	0-8	0

Segs = Segmented neutrophils

Bands = Band neutrophils

Lymphs = Lymphocytes

Monos = Monocytes

ERYTHROCYTE SEDIMENTATION RATES AND RETICULOCTE COUNTS

Sr. No.	Age	Values
1. Sedimentation rate, Westergren	Children Adult males Adult females	0-20 mm/hour 0-15 mm/hour 0-20 mm/hour
2. Sedimentation rate, Wintrobe	Children Adult males Adult females	0-13 mm/hour 0-10 mm/hour 0-15 mm/hour
3. Reticulocyte count	Newborns 1-6 months Adults	2-6% 0-2.8% 0.5%-1.5%

CEREBROSPINAL FLUID VALUES

1. Cell count		% PMNs
Preterm mean	9 (0-25.4 WBC/mm ³)	57%
Term mean	8.2 (0-22.4 WBC/mm ³)	61%
> 1 month	0.7	0
2. Glucose		
Preterm	24-63 mg/dL	mean 50
Term	34-119 mg/dL	mean 52
Children	40-80 mg/dL	
3. CSF glucose/blood glucose		
Preterm	55-105%	
Term	44-128%	
Children	50%	
4. Lactic acid dehydrogenase	5-30 units/mL	mean 20 units/mL
5. Myelin basic protein	< 4 ng/mL	
6. Pressure: Initial LP (mm H ₂ O)		
Newborns	80-110 (< 110)	
Infants/children	< 200 (lateral recumbent position)	
7. Respiratory movements	5-10	
8. Protein		
Preterm	65-150 mg/dL	mean 115
Term	20-170 mg/dL	mean 90
9. Ventricular	5-15 mg/dL	
10. Cisternal	5-25 mg/dL	
11. Lumbar	5-40 mg/dL	

IMMUNIZATION SCHEDULE IN CHILDREN

Recommendations of the INDIAN ACADEMY OF PEDIATRICS (IAP) Committee on Immunization

Age	Vaccines	Note
Birth	BCG OPV zero Hepatitis B-1	
6 weeks	OPV-1 + IPV-1/ OPV-1 DTPw-1/DTPa-1 Hepatitis B-2 Hib-1	OPV alone if IPV cannot be given
10 weeks	OPV-2 + IPV-2/ OPV-2 DTPw-2/DTPa-2 Hib-2	OPV alone if IPV cannot be given
14 weeks	OPV-3 + IPV-3/ OPV-3 DTPw-3/DTPa-3 Hepatitis B-3 Hib-3	OPV alone if IPV cannot be given Third dose of Hepatitis B can be given at 6 months of age
9 months	Measles	
15-18 months	OPV-4 + IPV-B1/ OPV-4 DTPw booster -1 or DTPa booster -1 Hib booster MMR-1	OPV alone if IPV cannot be given
2 years	Typhoid	Revaccination every 3-4 years
5 years	OPV-5 DTPw booster -2 or DTPa booster -2 MMR-2	The second dose of MMR vaccine can be given at any time 8 weeks after the first dose
10 years	Tdap HPV	Only girls, three doses at 0, 1-2 and 6 months
Vaccines that can be given after discussion with parents		
More than 6 weeks	Pneumococcal conjugate	3 primary doses at 6, 10, and 14 weeks, followed by a booster at 15-18 months
More than 6 weeks	Rotaviral vaccines	2/3 doses (depending on brand) at 4-8 weeks interval
After 15 months	Varicella	Age less than 13 years: one dose. Age more than 13 years: 2 doses at 4-8 weeks interval
After 18 months	Hepatitis A	2 doses at 6-12 months interval

1. The IAP endorses the continued use of cell pertussis vaccine because of its proven efficacy and safety. Acellular pertussis vaccines may undoubtedly have fewer side-effects (like fever, local reactions at injection site and irritability), but this minor advantage does not justify the inordinate cost involved in the routine use of this vaccine.
2. If the mother is known to be HBsAg negative, HB vaccine can be given along with DTP at 6, 10, 14 weeks/6 months. If the mother's HBsAg status is not known, it is advisable to start vaccination soon after birth to prevent perinatal transmission of the disease. If the mother is HBsAg positive (and especially HBeAg positive), the baby should be given Hepatitis B Immune Globulin (HBIG) within 24 hours of birth, along with HB vaccine.
3. Varicella, hepatitis A and pneumococcal conjugate vaccines should be offered only after one to one discussion with parents. Also refer to the individual vaccines notes for recommendations.
4. Combination vaccines can be used to decrease the number of pricks being given to the baby and to decrease the number of clinic visits. The manufacturer's instructions should be followed strictly whenever "mixing" vaccines in the same syringe prior to injection.
5. At present, the typhoid vaccine available in our country is the Vi polysaccharide vaccine. Revaccination may be carried out every three to four years.
6. Under special circumstances (e.g. epidemics), measles vaccine may be given earlier than 9 months followed by MMR at 12-15 months.
7. During pregnancy, the interval between the two doses of TT should be at least one month.
8. We should continue to use OPV till we achieve polio eradication in India. IPV can be used additionally for individual protection.
9. OPV must be given to children less than 5 years of age at the time of each supplementary immunization activity.

THE RECOMMENDED IMMUNIZATION SCHEDULES FOR PERSONS AGED 0 THROUGH 18 YEARS ARE APPROVED BY THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES ([HTTP://WWW.CDC.GOV/VACCINES/RECS/ACIP](http://www.cdc.gov/vaccines/recs/acip)), THE AMERICAN ACADEMY OF PEDIATRICS (<http://www.aap.org>), AND THE AMERICAN ACADEMY OF FAMILY PHYSICIANS (<http://www.aafp.org>).

Vaccine	Age										
	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years
Hepatitis B	Hep B	Hep B			Hep B						
Rotavirus			RV	RV	RV						
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP		DTaP				DTaP
Hemophilus influenzae type b			Hib	Hib	Hib	Hib					
Pneumococcal			PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus			IPV	IPV	IPV						IPV
Influenza					Influenza (Yearly)						
Measles, Mumps, Rubella						MMR					MMR
Varicella						Varicella					Varicella
Hepatitis A						Hep A (2 doses)				Hep A series	
Meningococcal										MCV	

Range of recommended ages for all children except certain high-risk groups.

Range of recommended ages for certain high-risk groups.

RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS.

Vaccine	Age		
	7-10 years	11-12 years	13-18 years
Tetanus, Diphtheria Pertussis		Tdap	Tdap
Human Papillomavirus		HPV (3 doses)	HPV Series
Meningococcal	MCV	MCV	MCV
Influenza	Influenza (Yearly)		
Pneumococcal	PPSV		
Hepatitis A	Hep A Series		
Hepatitis B	Hep B Series		
Inactivated Poliovirus	IPV Series		
Measles, Mumps, Rubella	MMR Series		
Varicella	Varicella Series.		

Range of recommended ages for all children except certain high-risk groups

Range of recommended ages for catch-up

Range of recommended ages for certain high-risk groups

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